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HEREDITY
IN HUMAN LEUKEMIA

AND ITS RELATION TO CANCER

TRANSLATED FROM DANISH

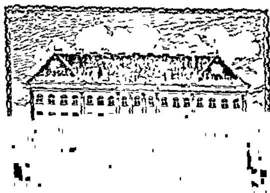
HEREDITY IN HUMAN LEUKEMIA

AND ITS RELATION TO CANCER

A GENETIC AND CLINICAL STUDY OF 209 PROBANDS

BY

AAGE VIDEBÆK



1947

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Denne Afhandling
er af det lægevidenskabelige Fakultet antaget
til offentlig at forsvares for den
medicinske Doktorgrad.

København, den 2 Juli 1947

MOGENS FOG,
h a dec

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Printed in Denmark

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Vald Pedersen Copenhagen

The researches which form the basis of the present volume were begun in 1945 during my service as private assistant to Prof. *Julius Engelbreth-Holm*, M.D., Director of the University Institute of pathologic Anatomy, and thanks to the excellent facilities for the work afforded me there and by Mr. *Tage Kemp*, M.D., as Head of the University Institute of human Genetics, they were completed already in 1946, and a preliminary account of the results published in the Acta Medica Scandinavica (vol. 127:26, 1947). I am sincerely indebted both to Prof. *Julius Engelbreth-Holm* and to Mr. *Tage Kemp* for their unfailing support and encouragement while the work was in progress.

I thank the Heads of the not less than thirty-seven different hospital services in Greater Copenhagen,—medical and children's services, policlinics and the Radium Center,—from which the patient material was collected, for the readiness with which access was given me to the case records on which its documentation is based, and Mr. *Johannes Clemmesen*, M.D., Director of the Cancer Registry, the excellent card index system of which made it easy for me to trace the cases of leukemia occurred in the last years. The assistance of Mr. *Th. Busk*, actuary to the Registry, has been of invaluable service to me in the solution of many of the statistical problems in connexion with the work.

I cannot deny myself the pleasure of publicly thanking my wife, *Iben Videbæk*, for the indefatigable interest and spirit with which she has helped me with the many archival researches and the vast correspondance involved by the work.

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To the Trustees of the *Anders Hasselbalch Anti-Leukemia Foundation* and *C. P. Schepler and Wife's Bequest, The Irma Foundation* I make acknowledgement of financial support toward the work.

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INTRODUCTION

"Patients have relatives"

Almost nothing is known of the causes responsible for leukemia in man. In a minority of cases it is probable that the disease may have resulted from exposure to roentgen rays or radium, in rare instances it is congenital. Sometimes one is tempted to associate its development with an antecedent polycytemia or pernicious anemia, but in the great majority of cases the etiology is unknown. The various theories that have been propounded may, in general, be rubricated under one of the following headings: that it is a malignant neoplasm; that it is due to some dysregulation or other, and is a deficiency disease, whereas the concept of it as the result of an infectious process has been abandoned. The correlation theory has been the object of renewed attention after the publication, by *Miller & Turner*, in 1944, of their observation of specifically acting substances in the urine of patients with leukemia, but further details must be waited for before it will be safe to build on these sensational discoveries, which perhaps do not at all exclude the concept of leukemia as a neoplasm. Also *Babes'* (1902) and *Ribbert's* (1904) conception of leukemia as a malignant neoplasm in blood-forming tissue is becoming more and more generally accepted by clinicians, because leukemias have been shown to resemble malignant tumors in an increasing number of ways. Especially on inbred strains of mice, which are good subjects for experimental cancer- and leukemia research, have many points of similarity between the two diseases and likenesses in their manner of reaction been demons-

Page

Chapter IV

GENETIC RELATION BETWEEN LEUKEMIA AND ENDOCRINE DISORDERS

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GENETIC RELATION BETWEEN LEUKEMIA AND CANCER

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trated. Acceleration- and cross-breeding experiments, particularly, carry weight in this respect.

So far, no investigation on a broad basis has been undertaken with a view to ascertaining if leukemia in man may be determined by hereditary factors; but it has seemed to me that such an investigation is called for, not only because it may in a new manner contribute to the understanding of the etiology of the disease in man, but also because it, considering the resemblance between cancer and leukemia, will be of interest to find out if hereditary factors play a rôle for the development of the latter disease in man, as it is known to be the case with regard to cancer, as shown by *Wainwright* (1931), *Waaler* (1932), *Wassink* (1935) and *Jacobsen* (1946), among others. At the same time, it will be of value to try to ascertain if the various forms of leukemia constitute a genetic entity, and if there genetically is any relationship between cancer and leukemia, or perhaps between leukemia and some particular form of cancer.

In the present work, I have tried to shed light on these problems. On the basis of a proband material comprising 209 patients with leukemia and, for comparison with these, 200 sound individuals in corresponding age classes, I have made it my object to determine the incidence of familial leukemia, and of other blood diseases and cancer among the relatives of the leukemia patients. Besides, I have, with a view to the concept of leukemia as a correlation disease, examined whether there in the families of the patients with leukemia was an unusually high incidence of diabetes mellitus and Graves' disease.

Chapter I

METHOD AND MATERIAL

1. METHOD

Examinations of twins and statistical genealogic investigations are the two principal methods employed in human genetic research. In connexion with the present study, the first of these methods is only of theoretical interest, because the occurrence of leukemia in one or both of a pair of twins is so rare that it has been impossible to obtain even a fairly adequate material for such examinations. In my statistical, genealogic investigations, I have used *Weinberg's* proband method, which has proved useful in other, similar investigations; thus, in Denmark, in those of *Strömgren* (1935), *Bartels* (1941) and *Jacobsen* (1946).

In collecting my material, I have therefore followed the pedigree chart used for proband investigations by the Danish University Institute of human Genetics, which comprises the following categories of relatives: parents, grandparents, paternal and maternal uncles and aunts, brothers, sisters and children The number of relatives of these categories was, on the average, about twenty for each proband. For practical reasons, my investigations were not extended to more distant relatives An attempt, to include for instance, cousins, male and female, or the brothers and sisters of the grandparents, would not only entail an enormous amount of work, but would not yield results in any way commensurate to the time and

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effort expended in it; because the information obtained, if any was forthcoming at all, would no doubt in the majority of cases be more or less uncertain.

With regard to the relatives included, the information sought comprised such data as, for the living, the age at the time of the inquiry, for the dead the age at the time of death and the cause of the latter; past and present operations and illnesses, especially cancer and other tumor diseases, blood- and splenic diseases, diabetes, Graves' disease, struma and myxedema. I ensured myself beforehand that the person interrogated knew the disease asked about; then I inquired if there had been any hospitalisations, and, if so, for what cause, and, with regard to the dead, about their condition during the last year of life. I explained what is understood by blood diseases, and that in relation to the investigations I was making I especially meant by such pernicious anemia and leukemia,— both of which conditions I found to be surprisingly well known. In order further to trace the occurrence of these diseases in the various families, I examined whether any special treatment had been instituted, especially roentgen- or radium therapy, or treatment with liver- or stomach preparations, thyroidin or insulin. As far as possible, I have sought my information by *personal questioning of the proband himself or his nearest* relatives; but as these as a rule were unable to give sure information about all the more distant relatives asked about, the research required, besides, a vast amount of correspondance with the latter or their descendants, or personal calls on them if they lived in, or near Copenhagen.

2 VERIFICATION OF THE INFORMATION OBTAINED

After I had thus got as much information as possible about all the above-named diseases among the various categories of relatives included in the research, the next step was to try to ascertain if the individuals referred to had really had those diseases. This made it necessary to obtain the data essential

in order to verify the supposed diagnoses of the cases noted, or sometimes merely suspected, of cancer, leukemia, pernicious anemia, other blood diseases, hyperthyreosis or myxedema. To get these, it was necessary to know the person's full name, address, date of birth, time and place of hospitalisation, and, if he had died, the place, date and year of his death. Not infrequently the information obtained in these respects was wrong or more or less incomplete; but in nearly all cases I succeeded in getting the errors corrected and the lacunæ filled out by inquiries to Public Registration Offices, searches in the files of the Internal Revenue Dep't or the burial authorities, and in the parish registers

As cancer very often takes a lethal course, the verification of cases of that disease is based chiefly on the death certificates, which are readily accessible in the State Record Office, where all such certificates from the whole country issued since 1919, and those issued in the provincial towns from about 1850 to 1920, are kept.

My inquiries resulted in information about 341 cases of cancer in the families of the 209 patients with leukemia. Of these 341 reported cancer patients, 58 had died in rural districts prior to 1920, and the diagnosis could therefore not be verified. In 261 of the remaining 283, the diagnosis of cancer could be verified, while in 22 (= 7.8 per cent) some other disease was given as the cause of death,—which does not, however, exclude the possibility that these individuals, too, may have had cancer, as supposed by the family.

In the families of the 200 non-leukemic controls, there had, according to the information given me, been 233 individuals with cancer Of these, 52 had died in rural districts prior to 1920, and the diagnosis could not be verified. With regard to 166 of the remaining 181 it was verified, while in the case of 15 (= 8 3 per cent) the death certificate or hospital record gave some other disease as the cause of death.

In order to test the extent to which my informants really had any knowledge of cases of diseases actually occurred in their families, I went through the death certificates for 387

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of the persons in the leukemia material whose deaths, according to the statements made to me, had not been due to any of the diseases particularly inquired about, and found that in none of them had the cause of death, in fact, been given as either cancer, blood disease, Graves' disease, myxedema or diabetes mellitus. In the same way, I also went through the death certificates for 300 persons in the control material who were not supposed to have died of cancer, and found only 4 in which the death had, after all, been due to that disease.

Examination with regard to the supposed cancer diagnoses showed them to be correct in 92 per cent of the cases. Examination regarding the causes of death of 687 persons not stated to have died of cancer showed this disease to have been present only in 0.58 per cent of them. Thus, the information given proved to have been even extremely reliable.

As we have seen, there were in the patient material 58, in the control material 52, cases of cancer, the statements about which could not be verified. As the information given had proved correct in over 90 per cent of the cases in which it was possible to control them, I have, however, taken also these 58 + 52 cases for good. With regard to relatives still living, the diagnoses have been verified by inquiry either to the patient's physician or to the hospital where the case has been treated. The number of cases of cancer of which I obtained information is, of course, the minimum of what may really have occurred of such cases in the family groups to which the investigation extended, still, I do not think that it falls very much short of the number actually diagnosticated. It is only comparatively few years since the number of cancer cases that got cured was so small that patients suffering from that disease as a rule died of it and the family could hardly be unaware of the fact. In recent years, on the other hand, many cancer patients get cured; but as a rule they have been hospitalised and it is so short time since they were ill that their relatives now living know, or have known them, and can tell about their disease, and their statements can be controlled by inquiry to

the hospital in question. The type of cancer which most readily escapes the attention of others is the early skin cancer, which is completely cured by a single ambulant treatment. Besides, there are of course the cases that may have either been wrongly diagnosed or not been recognised at all because the patient died of some other disease; and of which we therefore have no information.

As regards diabetes mellitus, Graves' disease, struma and myxedema, these diseases have of course sometimes a lethal issue and can then be verified either by means of the death certificate or the hospital records. On the other hand, there may have been many cases so slight, or of so passing nature, that they never came under medical, much less under hospital treatment. There may therefore no doubt have been a great many such cases about which I got no information. Those cases of diabetes mellitus of which I was told may however be taken for sure, because it is extremely rare that diabetes is confused with some other disease. Of the cases of Graves' disease, I have included only those where either the diagnosis could be verified or of which there from the description,—in some cases supported by photographs of the patient,—could be absolutely no doubt. The same applies to the cases of myxedema. Finally, I have, of the cases of blood diseases, included only those which could be verified, and have relied on the statement of the death certificate only where there was no hospital record. With regard to this group of diseases, I have furthermore sought information also from more distant relatives than those included in the pedigree chart.

3 MATERIAL

The investigation comprises 209 probands, patients with leukemia, and 200 sound individuals (control probands). The information about the relatives of both these groups was collected in exactly identical manner, as described in the preceding section

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a. *The Patients.*

All the probands were, or had been, patients in hospitals in Greater Copenhagen at some time or other during the period 1936-1945. Thanks to the good card-index system of the Copenhagen hospitals and in the last years also the excellent registration of cancer- and leukemia cases by the Danish Cancer Registry, it was not difficult to find records of a large number of patients with leukemia; especially as it might safely be assumed that all such patients in the Copenhagen area during that period had sooner or later been hospitalised.

b. *The Diagnosis.*

As most of the patients on whom the present study is based had died before my investigation was commenced, most of the diagnoses have been made on the basis of the existing case records. These were nearly all so fully informative, however, that the diagnosis of leukemia must be considered well founded; the more so because all the cases were treated within a period when especially the extensive use of both intravital and postmortem examinations had made the diagnostication of the disease much surer than before Necropsy had been performed on 66 per cent of the dead. On 56 per cent of the living either sternal or splenic puncture, or biopsy of lymph nodes had been done. Seventeen per cent of the patients I examined myself clinically and hematologically. In a great many cases no biposy will be needed, and an examination of the blood will suffice to make the diagnosis certain, no matter whether the case be one of *chronic lymphogenous leukemia* (with enlargement of lymph nodes, severe relative and absolute lymphocytosis in blood and bone narrow, and torpid course), *chronic myelogenous leukemia* (with enlargement of the spleen, marked leukocytosis with many immature forms, sparse erythropoiesis and good effect of roentgenologic treatment) or *acute leukemia* (with usually fatal affection of the upper respiratory tract, rapidly increasing anemia, hemorrhagic diathesis and, in most cases, severe leukocytosis, with im-

mature cell types dominating). The separation between acute and chronic leukemia is vague, but for the purposes of the present investigation I have chosen as criterion whether the disease was of under or over six months' duration As regards the most acute forms it is difficult, if not impossible, even for the most experienced to determine the type, because it as a rule is impossible to decide whether the dominating cells in the blood and bone marrow are myeloblasts, lymphoblasts or monoblasts The oxydase reaction (which incidentally has but seldom been tried) will not always settle the question, neither will the clinical picture of the case or examinations post mortem *Stem-cell leukemia* is the most relevant designation for this group of cases, though it thereby undoubtedly is made to include a variety of types. As it on the whole, also as regards the acute cases that presented a less acute course, often seems to have been rather a matter of chance whether the dominating immature cells were listed as lymphoblasts, myeloblasts or stem cells, it will often be practical and most correct to deal with all the cases presenting an acute course under the one heading of acute leukemia.

A few cases of *erythroleukemia* recorded are included because I, like *Forkner*, among others, consider such cases as a special manifestation of myelogenous leukemia

Cases of *subleukemic leukemia* have only been included when the records showed that biopsy had been performed. Such conditions as agranulocytosis, aplastic anemia, myelosclerosis, myelofibrosis (diagnoses which as a rule, but not always, exclude leukemia) and even leukemoid reaction, have not been considered

Nine cases have been excluded because, on closer examination, the original diagnosis could not be maintained.

1 —Radium Center (no 26259) Male When 20 years old gonorrhea and syphilis, never treated When 65 admitted with tumor of the epipharynx, hemoglobin 100 per cent, red cells 4,510,000 per cmm, white cells about 10,000, with 41 to 69 per cent of lymphocytes [illegible]

[illegible] bone

[illegible] of lymphocytes

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8—State Hospital (no. 53/43) Female, 44 years old Considerable enlargement of liver and spleen White cells 45,000 per cmm, many of them myelocytes Roentgen examination of the bones showed almost generalised sclerosis, however. Microscopy of fragment of a rib showed myelosclerosis with considerable fibrosis

9—Frederiksberg Hospital, service E. (no 1518/42) Female Admitted, 66 years old, after suffering for three months with diarrhea, fever, loss of weight, cough and sweating No enlargement of lymph nodes, spleen or liver, hemoglobin 39 per cent, red cells 1,680,000 per cmm, white cells 85,300, 90 per cent of which were lymphocytes At necropsy, no signs of leukemia were found, but caseous miliary tuberculosis.

c. *The Suitability of the Leukemia Patients as Probands.*

After I had thus, in the manner described, succeeded in collecting a large number of indubitable cases of leukemia, the next step was to use these cases as basis for a proband examination This made it necessary to find and interview the patients themselves or their nearest relatives, and also in this I succeeded in nearly all cases The patients, almost without exception, showed themselves willing to give the fullest possible information about their family, and as a rule also the relatives were obliging and understood the necessity of their personal assistance in getting the material collected.

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2.—State Hospital, service A (no 260/42) Male. Admitted, aged 70, with enlarged lymph nodes in neck, hemoglobin 107 per cent, white cells 23,000 (lymphocytes 61 per cent). Six years later: hemoglobin 130 per cent; white cells 10,200 (lymphocytes 18½ per cent). Sternal punctate: lymphocytes 5.6 per cent Three years later *perfectly well, no lymph node enlargement,* blood picture normal.

3.—Bispebjerg Hospital, service B (no 131/4/43) Female. Well until admitted, aged 75, with universal enlargement of the lymph nodes, up to walnut-size No enlargement of liver or spleen. Hemoglobin 69 per cent; red cells, 3,690,000 per cmm, white cells 14,500 (lymphocytes, 84 per cent) *Four years later, enormous enlargement of lymph nodes; white cells, 14,000,* lymphocytes, 41 per cent. Necropsy (no. 117/43). *Metastasising carcinoma of the liver;* no signs of leukemia.

4.—Gentofte County Hospital, service C (no. 1325/44) Male When 39 years old jaundice, with severe anemia and thrombopenia When 51 years old, tumor over right clavicle (Microscopy: simple hyperplasia). The spleen *reached the umbilicus. Hemoglobin 88 per cent; red cells 4,430,000 per cmm.,* white cells 21,800. Sternal punctate: lymphocytes, 51 per cent; lively erythropoiesis. The following year admitted with jaundice, universal enlargement of the lymph nodes, hemoglobin 38 per cent; red cells 1,550,000 per cmm, white cells 5740 (lymphocytes 56 per cent); sternal punctate showing *very strong erythropoiesis Necropsy (no. 525/45): no signs of leukemia.* The case diagnosed as *hemolytic anemia*

5.—Blegdam Hospital (no 566/44). Male At the age of 68 operated on for hypertrophy of the prostate The following year admitted with "angina", moderate universal enlargement of the lymph nodes, the apex of the spleen palpable just below the costal margin Hemoglobin 80 per cent, red cells *4,120,000 per cmm, white cells 17,000 (maximum 66,000),* segmented eosinophils 5 per cent, segmented neutrophils 33 per cent, lymphocytes 14 per cent. Sternal punctate: *eosinophils 36 per cent Meinicke and presumptive* Kahn tests strongly positive Bunnel's test agglutination in five tubes. Necropsy: no signs of leukemia *Sepsis*

6.—State Hospital, med policlinic (no 2243/37) Female Since the age of 34 *constant anemia resistant to both iron- and liver therapy When 41* found to be suffering from enlarged liver Six years later: Splenomegaly, hemoglobin 70 per cent, white cells *3840* per cmm (*myeloblasts 17* per cent, promyelocytes, 3 per cent). Thirty-seven roentgen films of the bone system showed rather diffuse *osteosclerosis,* verified by biopsy

7.—Sundby Hospital, service M. (no 1000/40) Boy At the age of 12 *he had a splenectomy performed for hemorrhagic purpura* Six months later: universal enlargement of the lymph nodes, the liver palpable 5 cm below the costal margin. White cells *116,400 per cmm (myelocytes 6 per cent, staff* cells 8 per cent, segmented neuthrophils 79 per cent) The necropsy (no 143/44) showed *purulent meningitis*

8.—State Hospital (no 53/43) Female, 44 years old Considerable enlargement of liver and spleen. White cells 45,000 per cmm, many of them myelocytes Roentgen examination of the bones showed almost generalised sclerosis, however. Microscopy of fragment of a rib showed *myelosclerosis* with considerable fibrosis

9.—Frederiksberg Hospital, service E. (no 1518/42) Female. Admitted, 66 years old, after suffering for three months with diarrhea, fever, loss of weight, cough and sweating. No enlargement of lymph nodes, spleen or liver, hemoglobin 39 per cent, red cells 1,680,000 per cmm, white cells 85,300, 90 per cent of which were lymphocytes At necropsy, no signs of leukemia were found, but caseous miliary tuberculosis

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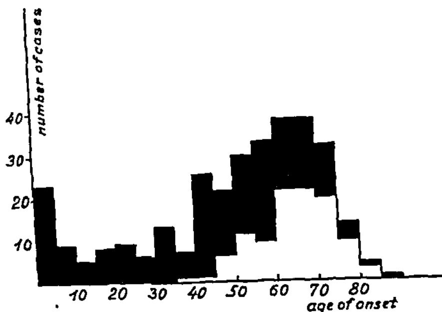


Figure 1.—Chart showing the distribution by age (at the time when the disease was ascertained) of 310 non-selected leukemia patients (■) and of the 101 of these (□) who were not included in the final proband material

from this that the 209 probands left would give a wrong picture of leukemia in general, but from Table 1, for instance, it will be seen that the distribution per cent of the different types of the disease is about the same for the originally collected 310 cases and the finally selected 209, and the same will be seen from Fig 2, which shows the age distribution for each of the two groups

Stem-cell leukemia occurs almost exclusively in children, and about the relatives of these it was therefore nearly always possible to get the necessary information, so that only two cases of this type had to be excluded. The proportion of patients representing this group among the final proband material is therefore a little higher than it rightly ought to be. The proportion of patients with chronic lymphogenous leukemia is slightly less than really desirable, because the age incidence curve for this type shows a maximum about the sixty-fifth year

sometimes necessary to exclude a prospective proband, because his informations seemed too vague or not sufficiently reliable. The result of a proband examination like the one here outlined depends to a great extent on the subjective factor; on the one hand on the collector of the data required: whether he follows the same method throughout, is capable of finding out by his leading questions if there among the relatives of the person interviewed are any cases of the diseases in which he is interested and is equally persistent in his search for information about all the different categories of relatives; on the other hand, and not least, on the person interviewed: whether he can be made to understand the purpose of the investigation in such a manner that he becomes interested in imparting all his knowledge, and, if necessary, in helping to get it supplemented with the data lacking. I have therefore made the whole investigation myself, both as regards the personal interviews and the necessary correspondance.

d. *Is the Patient Material adequate to the Purpose?*

After starting with a collection of 310 cases of leukemic patients, I succeeded in getting sufficient data about 209 of them, while 101 had to be given up Of these 101, two were simply unwilling to give any information, a few others had either been adopted by strangers or had been born out of wedlock, or all their relatives were living abroad; but in most of the cases the reason was that most of their relatives had died years ago, and that they therefore knew nothing about them.

Leukemia in all its forms may occur at any time of life, but shows its maximum incidence in advanced age (Fig 1) Of course, elderly people will often know nothing,—or, because the still older members of the family have died, be unable to find out anything about,—what diseases their grandparents, uncles and aunts may have had, or the causes of their death Fig. 1 also shows the distribution, by age, of the 101 leukemia patients excluded from the final material It will be seen that most of them were fifty years old or more. It might appear

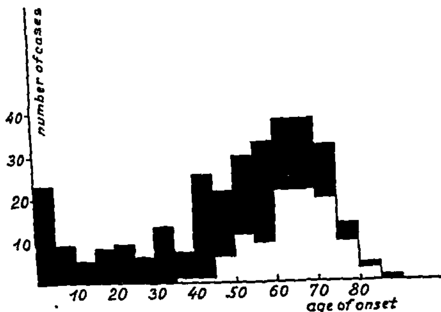


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of age (Fig. 2) and thus includes a particularly large number of old persons, many of whom were not able to furnish sufficient information and have therefore not been included in the final material.

TABLE 1.

Showing the Distribution of the different Types of Leukemia, and their Distribution by Sex, for 310 non-selected leukemic Patients and 209 leukemic Probands.

Type of Leukemia	Number of Cases among 310 leukemia Patients				Number of Cases among 209 Probands			
	Number	Per cent	Male	Female	Number	Per cent	Male	Female
Chronic lymphogenous	127	41.0	74	53	68	32.5	41	27
Chronic myelogenous	79	25 5	33	46	56	26 8	23	33
Acute lymphogenous	30	9 7	19	11	24	11 5	16	8
Acute myelogenous	27	8 7	15	12	17	8.1	11	6
Stem-cell	45	14 5	19	26	43	20 6	19	24
Monocytic	2	0 6	0	2	1	0 5	0	1
Total	310	100 0	160	150	209	100 0	110	99

The incidence distribution of the different types of leukemia shown in Table 1 for the 310 leukemia patients and the 209 probands, is calculated by means of the χ^2 test (*Fisher*, par. 21). As the χ^2 value by this calculation, with 4 degrees of freedom (the group: monocytic leukemia being left out of account), is found to be 5.61, which is equal to 30 % $>$ P $>$ 20 %, the differences in the distribution mentioned do not seem to negative the assumption that the 209 probands may be considered as representative as regards the distribution of the different types of leukemia.

Table 1 further shows the distribution by sex, of the patients in each of the four leukemia groups. That this distribution in the proband material corresponds to the usual sex incidence of leukemia is likewise seen from the Table, inasmuch as the application of the χ^2 test to the distribution by sex

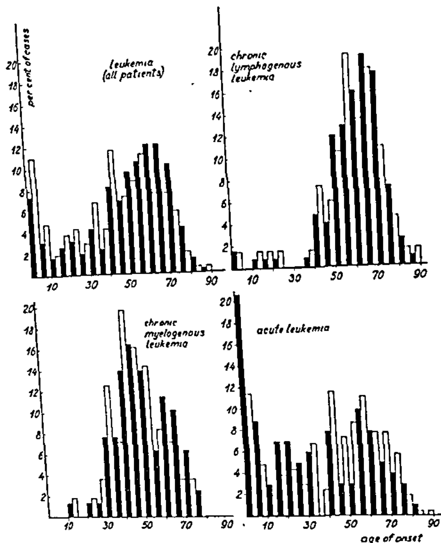


Figure 2 — Chart showing the distribution by age of 310 leukemia patients (■) 127 with chronic lymphogenous, 79 with chronic myelogenous and 102 with acute leukemia, compared with the age distribution of 209 probands (□) 68 with chronic lymphogenous, 56 with chronic myelogenous and 84 with acute leukemia.

for the different groups gives values which show good accordance for each of them.

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representative of leukemia in general, both as regards the representation of different varieties of the disease and the age- and sex incidence, and therefore a suitable material for the investigation with a view to which it was collected.

e. *The Control Material.*

Though it might seem an easy matter to find 200 normal subjects who would be a suitable basis for the control material, it proved to be a still more laborious task than that of collecting the patient material. To get in touch with 200 healthy individuals in other respects comparable to the leukemic patients was not in itself so difficult; the difficulty arose when it became a question of getting the desired information about their relatives. This was due especially to the circumstance that relatively few of the persons addressed,—in contrast to the leukemic patients or their relatives, in whose families there had been cases of so fatal a disease,—had, or could, in fact, be expected to have, any understanding of the scientific importance of the information asked for. Personally, they had no particular interest in the question of what diseases had occurred in their families, and in many cases they were not very willing to co-operate by seeking information from their relatives, neither did the investigator have the same natural basis as in the case of the leukemia patients, for addressing himself to these relatives in order to get information.

An attempt to obtain a sufficient material by inquiries to the functionaries of a large industrial concern failed, partly because only a few of those addressed were willing to co-operate, though the interviews could take place during their working hours and yet without loss of their pay; partly because it often in spite of repeated reminders was impossible to get the desired supplementary information. Nevertheless, I succeeded in getting from among the employees of this concern 47 pedigrees that could be used.

Among the residents of "De Gamles By" (a municipal institution in Copenhagen for the housing and care of indigent

TABLE 2

Showing the Distribution by Age in the different Types of Leukemia, for 310 non-selected Patients and 209 Probands.

<table>
<tr><th rowspan="2">Age</th><th colspan="2">All Types</th><th colspan="2">Chronic lymphogenous Leukemia</th><th colspan="2">Chronic myelogenous Leukemia</th><th colspan="2">Acute Leukemia</th></tr>
<tr><th>Among 310 non-selected patients</th><th>Among 209 probands</th><th>Among 301 non selected patients</th><th>Among 209 probands</th><th>Among 310 non-selected patients</th><th>Among 209 probands</th><th>Among 310non-selected patients</th><th>Among 209 probands</th></tr>
<tr><td>0— 4</td><td>23</td><td>23</td><td rowspan="8">6</td><td rowspan="8">5</td><td rowspan="7">9</td><td rowspan="7">11</td><td>21</td><td>22</td></tr>
<tr><td>5— 9</td><td>9</td><td>9</td><td>9</td><td>9</td></tr>
<tr><td>10—19</td><td>13</td><td>13</td><td>10</td><td>10</td></tr>
<tr><td>20—24</td><td>9</td><td>9</td><td rowspan="2">12</td><td rowspan="2">11</td></tr>
<tr><td>25—29</td><td>6</td><td>6</td></tr>
<tr><td>30—34</td><td>13</td><td>13</td><td rowspan="2">6</td><td rowspan="2">6</td></tr>
<tr><td>35—39</td><td>7</td><td>6</td></tr>
<tr><td>40—44</td><td>25</td><td>24</td><td rowspan="2">17</td><td rowspan="2">15</td><td rowspan="2">11</td><td rowspan="2">10</td></tr>
<tr><td>45—49</td><td>21</td><td>15</td><td rowspan="2">11</td><td rowspan="2">9</td></tr>
<tr><td>50—54</td><td>29</td><td>18</td><td>13</td><td>9</td><td rowspan="2">13</td><td rowspan="2">8</td></tr>
<tr><td>55—59</td><td>32</td><td>23</td><td>15</td><td>7</td><td>11</td><td>8</td></tr>
<tr><td>60—64</td><td>37</td><td>16</td><td>16</td><td>13</td><td rowspan="5">29</td><td rowspan="5">13</td><td rowspan="4">20</td><td rowspan="4">8</td></tr>
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<tr><td>70—74</td><td>31</td><td>12</td><td>24</td><td>12</td></tr>
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<tr><td>Total</td><td>310</td><td>209</td><td>127</td><td>68</td><td>79</td><td>56</td><td>102</td><td>84</td></tr>
<tr><td>χ^2</td><td colspan="2">17 57</td><td colspan="2">4 33</td><td colspan="2">3 81</td><td colspan="2">4 85</td></tr>
<tr><td>f</td><td colspan="2">14</td><td colspan="2">7</td><td colspan="2">4</td><td colspan="2">7</td></tr>
<tr><td>P</td><td colspan="2">$30\% > P > 20\%$</td><td colspan="2">$80\% > P > 70\%$</td><td colspan="2">$50\% > P > 30\%$</td><td colspan="2">$70\% > P > 50\%$</td></tr>
</table>

That also each of the various types of leukemia is well represented in the proband material is seen from the good accordance *between the age distributions for patients with the same type in the non-selected group and the proband group* (Table 2; Fig. 2)· χ^2 for each type group being so small that the difference in the age distribution is insignificant.

The proband material must thus be said to be adequately

same age as the relatives of the leukemia patient. In other words, there must be good accordance between the distribution by age of the relatives of the two groups. By age is understood in this connexion, for the living the age at the time of examination, for those who have died the age at the time of death.

TABLE 3.

Showing the Age Distribution for the different Categories of male Relatives in the Patient- (I) and the Control (II) Materials.

Age	Fathers		Paternal grand-fathers		Maternal grand-fathers		Paternal uncles		Maternal uncles		Brothers		Sons	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
0—4							27	18	17	9	47	54	10	7
5—9							5	3	4	5	15	11	15	14
10—14							7	3	3	3	13	9	12	11
15—19							4	6	10	6	11	11	11	6
20—24	1		2		1		14	11	10	16	22	17	22	13
25—29	6	3	1	1	4	2	14	14	20	18	21	12	20	15
30—34	7	8	3	1	2	5	17	13	20	15	26	17	19	14
35—39	9	12	10	2	6	4	20	17	22	28	36	29	22	18
40—44	12	12	6	1	4	5	15	16	21	25	32	32	12	21
45—49	12	13	8	8	5	4	27	26	26	31	32	47	14	14
50—54	17	18	11	6	11	10	28	15	22	26	36	30	11	3
55—59	21	21	10	10	11	16	35	28	31	23	36	20	2	4
60—64	17	18	18	19	21	18	45	38	37	24	42	22		1
65—69	26	18	26	25	28	30	43	38	49	32	43	31		
70—74	25	24	30	30	33	21	32	40	41	45	22	20		
75—79	31	27	22	29	17	28	28	28	33	45	14	24		
80—84	15	16	10	24	25	14	30	32	26	21	8	6		
85	9	10	25	22	11	18	18	17	10	14	1	1		
Total	208	200	182	178	179	175	412	363	402	386	457	393	170	141
f	11		9		9		15		15		16		10	
χ^2	2,57		27,12		9,46		8,95		17,92		22,11		7,28	
P	99 % > P		1 % > P > 1 ‰		90 % > P > 80 %		90 % > P > 80 %		50 % > P > 30 %		20 % > P > 10 %		70 % > P > 50 %	

By application of the χ^2 test I have examined how far there within each category of relatives was accordance between the age distribution in the two materials: patients and controls. As Tables 3 and 4 show, there was good accordance

elderly persons of both sexes), I obtained 37 control probands, who moreover presented the advantage that they all shortly before had passed through the local hospital for thorough medical examination. Yet it was difficult also from these to get the necessary information, especially owing to lack of interest or to their failing memory.

Gradually I realised that to obtain the remaining 116 controls I would have to seek them among such sound individuals as could be made to take an interest in contributing to the research work in hand, and these I found among the personnel of the University Institute of Human Genetics and the University Institute of Pathologic Anatomy, and, not least, among my own acquaintances, who in their turn found others, equally interested.

The control material was collected in Copenhagen during the period from October, 1945, to September, 1946. It comprises 200 individuals, who all have been able to give or procure such information as was required; which is to say that it should be just as full as that obtained with regard to the leukemic patients; and as far as possible it has been verified in exactly the same manner as the information pertaining to these. Only such individuals have been used as believed themselves perfectly sound and had never had any blood disease, chronic disease, malignant or dyscrinous affection. The material has been deposited in the University Library, Section II.

f. *Is the Control Material satisfactory?*

A control material, to be satisfactory, must be composed of subjects not only sound but in every other respect as far as possible corresponding to the leukemic proband material. The incidence of diseases which seldom manifest themselves already at birth, but only at some later time of life, is closely related to the age of the individuals. When a certain incidence of disease can be demonstrated in relatives of a patient with leukemia, it is imperative that the control be sought among such relatives as at the time of the examination are of the

same age as the relatives of the leukemia patient. In other words, there must be good accordance between the distribution by age of the relatives of the two groups. By age is understood in this connexion, for *the living the age at the time* of examination, for those who have died the age at the time of death.

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25—29	6	3	1	1	4	2	14	14	20	18	21	12	20	15
30—34	7	8	3	1	2	5	17	13	20	15	26	17	19	14
35—39	9	12	10	2	6	4	20	17	22	28	36	29	22	18
40—44	12	12	6	1	4	5	15	16	21	25	32	32	12	21
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50—54	17	18	11	6	11	10	28	15	22	26	36	30	11	3
55—59	21	21	10	10	11	16	38	28	31	23	36	20	2	4
60 - 64	17	18	18	19	21	18	45	38	37	24	42	22		1
65—69	26	18	26	25	28	30	43	38	49	32	43	31		
70 - 74	25	24	30	30	33	21	32	40	41	45	22	20		
75—79	31	27	22	29	17	28	28	28	33	45	14	24		
80—84	15	16	10	24	25	14	30	32	26	21	8	6		
85	9	10	25	22	11	18	18	17	10	14	1	1		
Total	208	200	182	178	179	175	412	363	402	386	457	393	170	141
f	11		9		9		15		15		16		10	
χ^2	2,57		27,12		9,46		8,95		17,92		22,11		7,28	
P	99 % > P		1 % > P 1 ‰		90 % > P > 80 %		90 % > P > 80 %		50 % > P > 30 %		20 % > P > 10 %		70 % > P > 50 %	

By application of the χ^2 test I have examined how far there within each category of relatives was accordance between the age distribution in the two materials: patients and controls As Tables 3 and 4 show, there was good accordance

TABLE 4

Showing the Age Distribution for the different Categories of female Relatives in the Patient- (I) and the Control (II) Materials

Age	Mothers		Paternal grand-mothers		Maternal grand-mothers		Paternal aunts		Maternal aunts		Sisters		Daugh-ters	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
0—4							23	19	11	16	52	49	5	18
5—9							1	7	9	3	17	12	11	8
10—14							4	3	4	1	18	9	8	12
15—19							2	3	10	5	13	4	11	8
20—24	2	3			1	1	10	6	6	10	18	20	19	15
25—29	9	7	3	4	4	2	14	8	13	12	23	16	19	21
30—34	8	17		5	6	4	10	15	21	15	26	15	19	15
35—39	14	11	5	6	8	4	15	15	28	15	28	19	20	15
40—44	11	9	8	4	8	3	25	17	19	19	24	27	22	7
45—49	8	15	7	6	6	4	21	25	23	25	42	30	11	13
50—54	8	7	5	6	8	7	25	25	23	12	21	39	8	4
55—59	17	12	15	5	9	10	41	28	20	21	42	45	2	2
60—64	20	19	18	18	19	21	38	25	38	24	32	36		
65—69	22	22	20	37	23	23	45	30	53	47	39	41		
70—74	35	26	31	19	27	31	60	44	40	36	30	30		
75—79	17	15	34	29	26	35	43	34	40	36	11	14		
80—85	19	18	26	12	20	26	26	28	43	27	10	3		
85	19	19	18	19	25	20	20	15	16	26	1			
Total	209	200	190	170	190	191	423	347	417	350	447	409	155	138
f	12		9		9		15		15		14		10	
χ^2	8,22		20,69		16,55		11,93		20,84		21,30		18,85	
P	80% > P > 70%		2% > P > 1%		10% > P > 5%		70% > P > 50%		20% > P > 10%		10% > P > 5%		5% > P > 2%	

except in the three categories: paternal grandfathers, paternal grandmothers and daughters The difference in the age distribution of the paternal grandfathers is mainly due to the paternal grandfathers of the controls being older than those of the leukemic patients; the number of cancer cases among them may therefore perhaps be a little larger than desirable for an absolutely ideal control material. The difference in the age distribution of the paternal grandmothers, on the other hand, is due to the paternal grandmothers of the controls being a

little younger than those of the leukemia patients, and perhaps there are therefore a little fewer cancer cases among them. The slight difference in the age distribution in the two daughter groups is of no importance, since there are only 2 cases of cancer in this category of relatives.

Though the probands themselves are not included in the family groups, it may be of interest to note that the proportion of male probands to female in the patient material is 110 male to 99 female (= 1.11), in the control material 86 male to 114 female (= 0.75). This somewhat higher proportion of females in the control material is not significant, however ($\chi^2 = 3.42$; $f = 1$, $10\% > P > 5\%$). It has been claimed that women as a rule give better and fuller information about illnesses in a family than men, but even if this should be true it would not make any difference so far as the present investigation is concerned, because the information about the different families was in nearly all cases given by several persons of both sexes.

Like the leukemic patients, the control probands represent a great variety of professions and different social milieus. Also in verifying the control material, I examined the death certificates for a number of persons besides those who were stated to have died of the diseases particularly looked for (cf. Chapter I, section 2), and found that the information given me had been, on the whole, remarkably reliable.

The pedigrees of the 209 probands comprise, in all, 4041 relatives about whom more or less precise data were forthcoming, besides 179 (= 4.24 per cent) about whom no information could be obtained. The pedigrees of the 200 controls comprise 3641 relatives about whom some relevant information was had, plus 160 (= 4.21 per cent) about whom nothing was known. These figures show that the extent of the knowledge with regard to relatives within the range of relationship stipulated for the investigation was about the same for the two groups, and that the average number of known relatives of these categories was for each leukemia proband 19.3, for each control proband 18.2. This difference in the number of relatives of the probands and the controls is significant, and is

in a large measure due to the circumstance that a relatively large proportion of the controls were unmarried, and the two categories: sons and daughters are therefore numerically smaller in this group than in the leukemia group. As there among the children of the leukemia probands were hardly any diseases of importance in relation to the investigation of which there is question here, we may, however, leave these two categories out of consideration, and there will then be no significant difference between the average size of the pedigrees of the leukemia probands and the control probands.

As the control material thus corresponds to the patient material as regards both the age distribution of the different categories of relatives, the size of the families and the sex distribution, place of residence, occupation and social milieu it may safely be contended that the pedigrees of the controls are a good counterpart to the pedigrees of the leukemia patients.

Chapter II

HEREDITY IN LEUKEMIA

1 THE LITERATURE ON FAMILIAL LEUKEMIA

The literature records a considerable number of observations of familially occurring leukemia. A collective review of these, so far as they have been accessible to me, will be given in the following pages. Most of them are merely case reports, separately of no great value, but together they may perhaps make it possible to reach a conclusion with regard to the existence of a hereditary factor and its rôle for the production of leukemia in man. I have subjected them all to a critical evaluation, with the result that a great many communications have been rejected, either because of entire lack of documentation of the observations reported, or because the diagnoses, from the data given, must be supposed to be wrong.

a Doubtful Cases

The accurate knowledge of leukemia as a distinct pathologic entity dates from 1845, when 3 cases were described respectively by *Virchow*, *Bennett* and *Craigie*. Already some years after, in 1861, the first report of familial occurrence of the disease was published, by *Biermer*, who described two cases in the same family. It is now generally believed that his diagnoses were wrong, but his communication drew attention to the subject, and in the following years a steadily in-

creasing number of reports appeared about similar instances of familial occurrence, with two or more cases in the same family. Most of these publications are merely case reports; among the relatively few whose authors by their own findings were instigated to collect and critically review the earlier published cases of familial occurrence is a Danish study, by *Petri* (1933), who in the literature found described 28 instances of familial leukemia.

Petri with good reason rejected not only the ten cases published prior to 1908—*Biermer* (1861), *Casali* (1872), *Senator* (1882), *Eichhorst* (1885), *Cameron* (1888), *Greene* (1888), *Ortner* (1891), *Croq* fils (1901), *Jewett* (1901) and *Arnsperger* (1905)—but of the more recent also those of *Brandenberg* (1909), *Schmorl* (1911), *Barrenscheen* (1912), *Campbell* (1912), *Mannaberg* (1917), *Decapite* (1924) and *Brügger* (1927), and thus of the 28 reported cases finds only 11 acceptable as authentic. Of these 11, I shall in the following review further omit 4, reported respectively by *Hanzel, Barrenscheen* and *Hirschfeld* (2 cases).

Hanzel (1908) described a well-authenticated case of acute leukemia in a man aged 20 years, but his statement about a maternal uncle likewise reported as having died of acute leukemia is obtained at second hand, and all clinical data are lacking.

Barrenscheen (1912) described in full detail a case of acute leukemia in a woman 38 years old, but states about her brother only that he suffered from typical lymphogenous leukemia. The same case is reported, without supplementary data, by *Eppinger* (1911).

Hirschfeld (1925) reported two instances of familial leukemia. With regard to the first of these, he gives no data about blood examinations, in the second, the patient was a man, 63 years old, with lymphogenous leukemia, whose sister, according to the statements of the family, had died of the same disease.

Further details about these doubtful cases as well as about the other, authentic, 7 may be found in *Petri's* study, already

referred to. To his list of insufficiently substantiated cases may be added a number of others, most of them of more recent date.

Vollenweider (1914) reported an instance of familial leukemia in 3 sibs, who died respectively 7 hours, 11 days and 3 weeks old, while a fourth child of the same parents died already 1 hour after birth, with cutaneous hemorrhages and large abdomen On the three first, necropsy was performed. Both the father and the mother were healthy, and it is specially noted that neither of them had syphilis. The necropsy findings in the three cases were as follows:

1—Severe jaundice, aortic stenosis, patent ductus arteriosus, cardiac hypertrophy, infiltrates in the enlarged liver, petechiae in skin, mucous membranes and organs In kidneys and pancreas, circumscribed clumps of leukocytes, lymphocytes and myelocytes, in spleen and liver similar accumulations, but more diffuse, the leukocyte count in the blood increased

2—Severe jaundice and anemia, bile-colored urine, enlargement of the lymph nodes, liver and spleen Microscopy as in 1, except that the infiltrates consisted partly of erythroblasts.

3—Pronounced anemia, some jaundice, hemorrhages in the skin, considerable enlargement of the liver, slight enlargement of the spleen. Hemoglobin 15 per cent, white cells 14,000 per cmm (erythroblasts 5 per cent, neutrophils 47 per cent, lymphocytes 48 per cent) Microscopy of liver, spleen and thymus showed no signs of leukemia

Vollenweider diagnosed the disease in the first child as lymphogenous leukemia, in the second as myelogenous, in the third as mixed leukemia, but his diagnoses are hardly correct. All three children were undoubtedly suffering from erythroblastosis fetalis. Both the familial occurrence, the rapid termination in death, the anemia, the hemorrhagic diathesis and the severe jaundice, as well as the presence of erythroblasts in the blood and infiltrates, the leukocytosis and the extramedullary hematopoiesis in various organs,—which by *Vollenweider* was interpreted as leukemic infiltration,—speak for this diagnosis as the true one

Rosenhaupt (1915) reported a case of acute leukemia in a girl 20 months old, with hemorrhagic diathesis, enlargement of the lymph nodes and fever, following parotitis. The examination of the blood showed "einer der schwersten Fälle akuter Leukämie." According to second-hand information, the child's maternal grandmother had been cured of leukemia by treatment with roentgen rays.

Korteweg (1919) mentions the occurrence of myelogenous leukemia in a pair of twins a few months old, but only supplies satisfactory data with regard to one of them.

Decastello (1925) reported the observation of chronic myelosis in a young man, whose father's brother had died of acute leukemia, but presents no data to support his diagnosis.

Macciotta (1928) records a familial case of four brothers, three with acute, the fourth with subacute, lymphogenous leukemia; but his original communication has not been available, only a brief review of it, lacking the data on the basis of which the diagnoses were established.

Siegel (1928) reported an instance of lymphogenous leukemia in a pair of twins, boy and girl, two and a half years old. The correctness of his diagnoses is much to be doubted, however; especially as the children were discharged as improved. The blood examinations showed anemia, but otherwise nothing indicative of leukemia, since there were neither leukocytes, abnormal cell distribution nor enlargement of the liver or spleen.

Koehler (1929) described in detail a case of chronic myelogenous leukemia in a man 57 years old, and mentioned that a brother of this patient had died with the same symptoms, and that a sister was suffering from pernicious anemia, but he gives no particular information about the cases of these two relatives.

Naegeli (1931) recorded an observation of myelosis in a woman and chronic lymphadenosis in her brother.

Hering (1935) briefly noted: "64 jähr Dr. med Chronische lymphatische Leukamie. Vater 1888 53 jahrig an chronischer lymphatischer Leukamie gestorben (Sektion Prof. Thoma)", and

further says that *Jacques* has observed leukemia in a pair of twins.

Seiler (1935) published a well established case of erythroleukemia and adds, without giving any hematologic data, that the father of the patient had died of leukemia.

Curschmann (1936) found among 108 cases of leukemia only one instance in which the disease was familial, the patients being a father (1) and his son (2):

1.—Died, 50 years old, of chronic lymphogenous leukemia. The diagnosis stated to have been established hematologically and by necropsy in 1888.

2.—At the age of 59, enlargement of lymph nodes in neck and axillae, enlargement of the spleen, hemoglobin 91 per cent, white cells 28,000 per cmm. (lymphocytes 47 per cent).

Ardashnikov (1937) found among 33 probands two presumable instances of familial leukemia:

1.—Typical myelogenous leukemia in a woman 25 years old. Hemoglobin 60 per cent, white cells 230,000 per cmm. The blood picture myeloid. The *mother* stated that her brother had died of leukemia.

2.—Man, died, 46 years old, of lymphogenous leukemia. Hemoglobin 63 per cent, white cells 54,200 per cmm. (lymphocytes 95 per cent). The family stated that a male cousin had died, 45 years old, of leukemia.

The author also mentions a family with leukemia in two sisters, the father and a sister of the latter, but clinical data are presented only with regard to the case of one of the two sisters.

Shipton (1938) reported a typical case of myeloblastic leukemia in a woman 55 years old, and mentioned—but without giving any clinical data,—that a nephew of hers had died of the same disease. He also records a case of a boy, 7 years old, who after two months' illness died of subleukemic leukemia verified by necropsy, and whose father he from the information given by the mother believes to have died of the same disease.

Boggian (1938) found acute lymphogenous leukemia in a boy and his sister, and in a male cousin of theirs, respectively

20, 19 and 13 months old. Another sister developed chronic lymphogenous leukemia at the age af four years. (Cit. by *Cotti;* the original communication not available).

Mohr (1938) reported a typical case of lymphogenous leukemia in a man 48 years old; about a niece of his it is only stated that she developed acute lymphogenous leukemia at the age of four and a half years.

Hofmeier (1938) reported an instance of leukemia manifesting itself concordantly in a pair of enzygotic female twins. One of them died two and a half years old of lymphogenous leukemia after two months' illness; the other developed the same disease at the age of four years, and died in the course of three months. Shortly afterwards, a sister of their mother also died of lymphogenous leukemia. There are no clinical data.

Maack (1940) reported the necropsy findings in a case of leukemia in a boy four years old with splenomegaly, enormous enlargement of the liver and leukocytosis. The microscopic diagnosis was myelogenous leukemia. In his brother, the leukocyte count was normal, but myelocytes were present in the blood and there was marked shift to the left, which must, however, be considered as insufficient criteria for the diagnosis of myelogenous leukemia.

Gänsslen (1940) mentions, without giving any further data, an observation, by *Kraupse* (1939), of lymphogenous leukemia in two brothers.

Cicovacki (1940) found among 139 patients with leukemia only one instance of familial occurrence, a brother of one of them having, according to the statement of a physician, died of the same disease.

Postel (1942) gives some further details about an instance of familial leukemia already reported by *Weitz* (1940) A woman 58 years old developed subleukemic myelogenous leukemia, subsequently verified by necropsy. Seven years later, a sister of her, 61 years old, became ill with enlargement of the spleen and liver, and though neither the blood examination nor sternal and splenic punctures resulted in any observations indicative of leukemia, *Postel* thinks himself justified in diag-

nosing the case as such, merely on the basis of the likeness of the pathologic picture to that of the sister's disease.

Turpin (1944) mentions three families in which both leukemia and scleroderma occurred. In one of them there were two cases of acute leukemia, in two brothers, one of whom died sixteen years after the other. *Turpin* thinks that there is a genetic relationship between leukemia and scleroderma; but furnishes no documentation for his diagnoses of leukemia.

Rohr (1945) recorded a case of myeloblastic leukemia in a man whose sister's child was said to have died of leukemia.

Finally it may be mentioned that *Bie*'s observation (1910) of two cases of leukemia, in a man and his servant-girl, has mistakenly been referred to as an instance of familial occurrence.

It is regrettable that so many reports of several cases of leukemia in families do not contain sufficient clinical data or details of necropsy findings to make the diagnosis evident; all the more because many of the cases were no doubt carefully examined and a little greater attention to details in the published communications might have been a valuable help toward increasing the still rather small number of thoroughly proven instances of human familial leukemia.

b *Incontrovertible Instances of familial Leukemia.*

As already said, I shall in the present work consider 7 of the instances of familial leukemia listed by *Petri* as among the sufficiently elucidated; namely, those reported by *McGavran* (1922), *Rosenow* (1925), *Schereschewsky* (1926), *Vercellotti* (1926), *Weiss* (1927), *Riccitelli* & *Ragnotti* (1927) and *Dameshek, Savitz* & *Arbor* (1929)

To these must be added *Petri*'s own observation (1933) of chronic lymphogenous leukemia in two brothers·

I —When 52 years old enlargement of the lymph nodes Six months later, white cells 461,000 per cmm (lymphocytes 98 per cent), hemoglobin 80 per cent No enlargement of the spleen The blood picture persisted almost unchanged until death Observed for four years

2.—When 51 years old slight enlargement of the lymph nodes; the spleen and liver respectively 3 and 2 cm below the costal margin. Hemoglobin 17 per cent, white cells 31,000 per cmm (lymphocytes 83 per cent), increasing to 112,000 per cmm Two months later, white cells 7,682 per cmm. (lymphocytes 50 per cent, lymphoblasts 14 per cent). Four years later still living, subjectively well, with slight enlargement of the spleen, hemoglobin 91 per cent, white cells 4,080 (lymphocytes 23 per cent).

Petri thinks that there can be no doubt about the diagnosis. About the younger brother, *Gänsslen* (1940) believed that the case was not one of leukemia but of lymphatic reaction, because he mistakenly understood *Petri's* report as implying that the patient had been cured; but according to a communication from *Petri* to the author the man died, at the age of 64 years, of leukemia.

Morawitz (1933) records an instance of two brothers, whose cases he within an interval of three months diagnosed as lymphogenous leukemia.

1.—When 59 years old universal enlargement of the lymph nodes, tenderness of the bones, splenomegaly, hepatomegaly, hemoglobin 51 per cent, white cells 205,000 per cmm. (lymphocytes 99 per cent), thrombopenia Observed for five months

2.—When 57 years old universal enlargement of the lymph nodes, hemoglobin 80 per cent, white cells 119,000 (lymphocytes 90 to 95 per cent).

Steiner (1933) found among 134 leukemia patients one instance of familial occurrence: lymphogenous leukemia in a man (1) and four years later myelogenous leukemia in his brother (2).

1.—Age, 50 years Universal enlargement of the lymph nodes, splenomegaly; white cells 23,300 per cmm (lymphocytes 79 per cent) Microscopy of a lymph node showed leukemia

2.—Age, 58 years Splenomegaly, white cells 30,000 per cmm., with typical myeloid blood picture Roentgen-ray treatment was applied with good, but only transient effect

Wüllenweber (1937) reports two cases of chronic, respectively myelogenous and lymphogenous leukemia in a woman (1) and her sister (2); the former observed for two, the latter for three years. The same two cases were later published also by Winkler (1939).

1.—Age, 54 years. Splenomegaly; hemoglobin 45 per cent; white cells 108,000 per cmm. (myelocytes 52 per cent, metamyelocytes 6 per cent, staff cells 19 per cent, segmented neutrophils 10 per cent, lymphocytes 13 per cent).

2.—Age, 56 years. Lymph nodes in neck, axillae and groin, enlargement of the liver and spleen, hemoglobin 28 per cent, white cells 74,000 per cmm. (lymphocytes 100 per cent). Following roentgen-ray treatment, the white cell count was 13,000 per cmm., with 93 per cent of lymphocytes.

Schnyder (1937) reports two cases of myeloblastic leukemia in a young woman (1) and a daughter of one of her female cousins (2).

1.—At the age of 19 panaritium, four months later hemoglobin 72 per cent, white cells 4,970 per cmm. (myeloblasts 34 per cent, myelocytes ½ per cent, metamyelocytes ½ per cent, segmented neutrophils 14 per cent, eosinophils 2 per cent, basophils ½ per cent, monocytes ½ per cent, lymphocytes 48½ per cent). Gradually extensive necrosis in the pharynx. Spleen and liver only slightly enlarged. Necropsy showed myeloid infiltration in the organs.

2.—At the age of 6 severe anemia, splenomegaly, hemorrhagic diathesis, moderate enlargement of the lymph nodes, white cells 16,500 per cmm. (myeloblasts 71 per cent).

Ardashnikov (1937) collected a proband material of 33 leukemia patients, and thus found, besides two probable, one sure instance of familial occurrence: chronic myelogenous leukemia in a young man (1) and chronic lymphogenous leukemia in a brother of his father (2).

1.—Age, 30 years. Enlargement of the lymph nodes, liver and spleen; hemoglobin 39 per cent, white cells 147,800 per cmm. (myeloblasts 22

2.—When 51 years old slight enlargement of the lymph nodes; the spleen and liver respectively 3 and 2 cm. below the costal margin Hemoglobin 17 per cent, white cells 31,000 per cmm. (lymphocytes 83 per cent), increasing to 112,000 per cmm Two months later, white 'cells 7,682 per cmm (lymphocytes 50 per cent, lymphoblasts 14 per cent). Four years later *still living, subjectively well, with slight enlargement* of the spleen, hemoglobin 91 per cent, white cells 4,080 (lymphocytes 23 per cent).

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2—Age, 58 years Splenomegaly, white cells 30,000 per cmm, with typical myeloid blood picture Roentgen-ray treatment was applied with good, but only transient effect

1.—Age, 33 years. Hemorrhagic diathesis, hemoglobin 27 per cent, white cells 32,700 increasing to 250,000 per cmm., 80 per cent of which were oxidase-positive and judged to be early myeloblasts. At necropsy, leukemic infiltrations were found in the liver.

2.—The leukemia developed in association with "angina" when she was 25 years old. Hemoglobin 63 per cent, white cells 4600 per cmm (myeloblasts 90 per cent); sternal punctate: 74 per cent of myeloblasts. Necropsy confirmed the diagnosis.

Decastello (1939) added a sixth case of chronic lymphogenous leukemia to the five previously known in the family reported by *Weiss* already in 1911 and later described in greater detail by him in 1927.

1.—Woman, became ill in 1905 with marked splenomegaly, hepatomegaly and enlargement of the lymph nodes. White cells 64,800 per cmm. (lymphocytes 86 per cent), three years later, white cells 34,200 per cmm (lymphocytes 75 per cent). Observed for four years.

2.—Brother, became ill in 1896, with great enlargement of the liver, lymphogenous leukemia, particularly localised to the intestine: and severe diarrheas. Died five years later. No blood examinations.

3.—Brother, became ill in 1909 with increasing enlargement of the lymph nodes, enlargement of liver and spleen, white cells 48,000 to 64,000 per cmm (lymphocytes 74 to 80 per cent). Died two *years later*.

4.—Son of no. 1. Became ill in 1913, with gradual, universal enlargement of the lymph nodes and marked splenomegaly. White cells 64,600 per cmm (lymphocytes 50 per cent, transitional forms 15 per cent). Thirteen years later hemoglobin 55 per cent, white cell count 193,000 per cmm., with 94 per cent of lymphocytes. Died 1927.

5.—*Daughter of no. 1*. Became ill in 1924, with enlargement of submaxillary lymph nodes, hemoglobin 75 per cent, white cells 8700 per cmm. differential cell count normal. Four months later hemoglobin 66 per cent, white cell count 6,100 per cmm. (lymphocytes 2 per cent, neutrophils 88 per cent).

6.—(The case reported by *Decastello*). Daughter of no. 3. At the age of 48 enlargement of liver and spleen, white cells 140,000 per cmm. (lymphocytes 95 per cent). Duration of the disease about two years.

As regards nos. 1, 3, 4 and 6 there can be no doubt about the

per cent, promyelocytes 2 per cent, myelocytes 5 per cent, basophils 15 per cent, eosinophils 2 per cent, *staff cells* 21 per cent, *segmented* neutrophils 31 per cent). The case was observed for three years and the diagnosis verified by necropsy.

2.—At the age of 60 years considerable enlargement of the lymph nodes, liver and spleen; white cells 70,000 per cmm (lymphocytes 90 per cent) Five years later, white cells 20,000 per cmm, with 90 per cent of lymphocytes.

Shipton (1938) reports an instance of myeloblastic leukemia in a woman (1) and her son (2).

1.—Age, 50 years Suggillations, edemas, considerable enlargement of the liver. White cells 21,000 per cmm, with 82 per cent of myeloblasts, rising to 188,000 per cmm, with 95 per cent of myeloblasts Died after six weeks' illness The diagnosis confirmed by necropsy

2—Age, 15 years Severe anemia, epistaxis and fever "The blood pictures are those of a myeloid leuchaemia with many cells of a very primitive type. Postmortem histological examination confirmes this diagnosis."

Gottlebe (1938) reports the occurrence of myeloblastic leukemia in two sisters.

1—Age, 60 years Deglutition difficult, fever, hemorrhagic diathesis, cutaneous hemorrhages and hematuria Hemoglobin 62 to 35 per cent, white cells 2,350 to 4,050 per cmm (myeloblasts 49 per cent, staff cells 2 per cent, *segmented* neutrophils 8 per cent, lymphocytes 42 per cent, monocytes 1 per cent) Died after two weeks' illness No necropsy

2—Age, 60 years Splenomegaly, moderate enlargement of the lymph nodes, hemorrhagic diathesis, ulcerations in the oral cavity Hemoglobin 50 per cent, white cells 18,900 per cmm (myeloblasts 97 per cent, promyelocytes 3 per cent) Died after two weeks illness The diagnosis verified by necropsy.

Laub (1939) reports the observation of myeloblastic leukemia in a woman (1) and in her daughter (2), who died fifteen years later of the same disease.

author, the man eventually died, however, of myelogenous leukemia.

1—Treated for two years with blood transfusions for a hyperchromic megaloblastic anemia—called "achrestic" anemia—which did not respond to treatment with iron-, liver- or stomach preparations The bone marrow was megaloblastic, there was no gastric achylia After the patient had been ill for three years, there came enlargement of the spleen, and the white cell count rose to 143,000 per cmm, with many *immature myeloid* cells Death supervened after 5 years' illness, the necropsy confirmed the diagnosis of myelogenous leukemia

2—Tonsils large and ulcerating, lymph nodes enlarged, eventually hemorrhagic diathesis Hemoglobin 22 per cent, white cells 64,500 per cmm (stem-cells 70 per cent, peroxidase-negative, *myelocytes* 1½ per cent, metamyelocytes 2 per cent, segmented neutrophils 21 per cent, lymphocytes 5½ per cent) The patient died after twelve days' illness; the necropsy showed leukemic infiltration in lymph nodes, spleen, bone marrow and liver

Cotti (1941) describes familial occurrence of leukemia in an Italian family, with three authentic cases of the disease in a woman (1), her daughter (2) and a grandson (3) of the mother's sister Another sister of the mother died, 42 years old, of a mediastinal tumor described as Hodgkin's disease. The mother's mother had probably died of leukemia.

1—Age, 45 years Splenomegaly Hemoglobin 48 per cent, white cells 60,000 per cmm (myeloblasts 5 per cent, promyelocytes 4 per cent, neutrophil myelocytes 24 per cent, segmented neutrophils 65 per cent). Thirteen months later, shortly before death, hemoglobin 40 per cent, white cells 136,000 per cmm

2—Age 23 years Splenomegaly, hepatomegaly, tenderness of the bones Hemoglobin 75 per cent, white cells 69,000 per cmm (myeloblasts 3 per cent, promyelocytes 5 per cent, metamyelocytes 6 per cent, basophils 6 per cent, segmented neutrophils 62 per cent) Good benefit from roentgen-ray treatment Nine months later hemoglobin 63 per cent, white cells 84,000, with many immature myeloid cells

3—Age, 5 years Enlarged lymph nodes in neck, splenomegaly, hemorrhagic diathesis Hemoglobin 18 per cent, white cells 30,000 per cmm (lymphocytes 90 per cent) Two months later, shortly before death,

correctness of the diagnosis. About no. 2 the data are too few, and about no. 5 *Weiss* admits that if we look at the case by itself there is not sufficient evidence for the diagnosis of leukemia, but that it is warranted in view of the familial anamnesis. This argument is hardly acceptable, and I therefore consider only four of the cases as proven, leaving out nos. 2 and 5.

Jelke (1940) demonstrated acute leukemia in a pair of enzygotic twins about 5 months old.

1—Bleeding of the gingivæ, large liver and spleen, hemoglobin 54 per cent, white cells 735,000 per cmm (lymphblasts 17 per cent, large lymphocytes 29 per cent, small lymphocytes 52 per cent,—all oxidase-negative). Large lymphocytes dominating in the sternal punctate Died after twelve weeks' illness The diagnosis confirmed by the necropsy.

2—At admission pronounced anemia, convulsions, liver and spleen enlarged Hemoglobin 32 per cent, white cells 1,027,000 per cmm (lymphoblasts 9 per cent, large lymphocytes 22 per cent, small lymphocytes 69 per cent) The sternal punctate composed chiefly of lymphocytes of all grades of maturity Died of cerebral hemorrhage after two weeks' illness At necropsy, leukemic infiltration was found in the liver and myocardium

Maack (1940) describes two cases of typical lymphogenous leukemia in two brothers; a third brother had squamocellular carcinoma.

1—Age, 63 years White cells 22,400 per cmm (lymphocytes 75 per cent) Six months later enlargement of the lymph nodes, splenomegaly, white cells 45,400 per cmm (lymphocytes 94 per cent)

2—Age, 46 years Enlargement of the lymph nodes, splenomegaly, white cells 25,000 per cmm (lymphocytes 100 per cent) Temporary remission following treatment with roentgen rays

Bichel (1940) reported a case of "achrestic anemia" in a man 32 years old (1) and stem-cell leukemia in his sister, aged 27 years (2). According to a communication from *Bichel* to the

the liver enlarged Hemoglobin 55 per cent, white cells 201,000 per cmm (monocytes 86 8 per cent, monoblasts 2 5 per cent) No necropsy.

2.—Age, 43 years Had been feeling fatigued for four months when hemorrhagic diathesis developed, there came ulceration of the *fauces* and swelling of the lymph nodes in the neck. Hemoglobin *51 per cent*, white cells 88,000 per cmm, (myeloblasts 92 6 per cent) Sternal punctate 92 per cent of myeloblasts No necropsy

Hogrefe (1945) describes chronic myelogenous leukemia in a woman (1) and her sister (2), and plasmocytic reticulosarcoma in a twenty-*four-year-old son of another* sister.

1—Age, 49 years Swollen lymph nodes in the neck and enlargement of the liver and spleen Hemoglobin 82 per cent, white cells 12,000 per cmm (myeloblasts 2 6 per cent, promyelocytes 0 6 per cent, myelocytes 11 6 per cent, metamyelocytes 9.3 per cent, segmented neutrophils 64 6 per cent, lymphocytes 5 6 per cent, monocytes 2.3 per cent) Some good effect *from roentgen-ray treatment. Shortly before death*, hemoglobin 68 per cent, white cells 5,720 per cmm, immature myeloid cells 52.5 per cent) Observed for fifteen years

2—Age, 40 years. Increasing fatigue, loss of weight, hemorrhagic diathesis, splenomegaly Hemoglobin 70 per cent, white cells 6,400 per cmm (myeloblasts 15 per cent, myelocytes 14 per cent, segmented neutrophils 63 per cent, basophils 3 per cent, lymphocytes 5 per cent) Good effect from roentgen-ray treatment. About a year later, hemoglobin 48 per cent, white cells 50 000 (myeloblasts 66 per cent) Necropsy confirmed the diagnosis of myelogenous leukemia

Rohr (1945) and *Moeschlin & Rohr* (1939) report two instances of familial occurrence of leukemia.

I—Chronic myelogenous leukemia in a woman (1) and her mother (2), and chronic lymphogenous leukemia in the mother's sister (3).

1—Age, 47 years Increasing enlargement of the spleen, rising white cell count (to 300,000 per cmm) and falling hemoglobin values Differential count *myelocytes* 42½ per cent, staff cells 9½ per cent, segmented neutrophils 45 per cent, eosinophils 1½ per cent, basophils 4 per cent, monocytes 2½ per cent, lymphocytes 4½ per cent For a time good effect of roentgen-ray therapy. Observed for two years Necropsy showed leukemic infiltration in liver and spleen

hemoglobin 18 per cent, white cells 6,600 per cmm, with 99 per cent of lymphocytes

Lossen (1942) reports an instance of chronic myelogenous leukemia in a father (1) and acute myeloblastic leukemia in his son (2).

1.—Age, 66 years Considerable enlargement of the spleen, hemoglobin 58 per cent, white cells 151,000 per cmm. (myeloblasts 18 per cent, myelocytes 20 per cent, metamyelocytes 12 per cent, staff cells 1 per cent, segmented neutrophils 32 per cent, basophils 2½ per cent, lymphocytes 5 per cent).

2—Age, 29 years. Gastric hemorrhages, enlargement of the liver, hemoglobin 70 per cent, white cells 171,000 per cmm (myeloblasts 87.5 per cent, myelocytes 2 per cent, metamyelocytes 1 5 per cent, staff cells 1 per cent, segmented neutrophils 3 5 per cent, lymphocytes 4 5 per cent). Necropsy showed myeloblastic infiltration in liver, spleen and bone marrow

Hornbaker (1942) describes in detail the course of a chronic leukemia in three sisters

1—Age, 39 years Lymph nodes enlarged, white cells 18,000 per cmm (lymphocytes 64 to 70 per cent) Died after one year s observation

2—Age, 55 years Lymph nodes enlarged, white cells 36,800 per cmm (lymphocytes 80 per cent) Died after a year and nine months observation No necropsy

3—Age, 55 years Pronounced splenomegaly White cells 162,000 per cmm (myeloblasts 8½ per cent, myelocytes 30 per cent) Observed for a year and nine months

Meikle (1944) describes two familial cases: monocytic leukemia in a man (1) and myeloblastic leukemia, developed two years later, in his sister (2).

1.—Age, 46 years Had been feeling fatigued for a couple of months when his tonsils became swollen and covered with large pseudomembranous coatings, the lymph nodes in the neck, too, became swollen and

On the other hand it has also been asked if the familial occurrence might not be merely incidental. *Petri* (1933) says that theoretically there is a possibility that in Denmark two cases of leukemia may occur quite incidentally in the same family about once in every three years, but he does not examine how often this really happens to be the case. *Rosenow* (1925), *Steiner* (1933), *Curschmann* (1936) and *Cicovacki* (1940) each found only a single instance of familial occurrence among materials of respectively 125, 134, 108 and 139 leukemia patients, which would make it seem that leukemia in families is exceedingly rare. One has the impression, however, that they obtained these figures simply by going through the case records of various hospital services with a view to ascertaining how often they contained notices about occurrence of leukemia in the families concerned,—an examination which is of no value in this connexion *Ardashnikov* (1937) made investigations with regard to the families of 33 leukemia patients and found one sure and two probable instances of familial occurrence, and he concluded from this that hereditary factors may play a rôle for the development of human leukemia.

From all that is known up to the present it must thus be admitted that although a certain number of authentic observations of at least two cases of leukemia in the same family have been made, there has been no evidence to prove that this familial occurrence was not incidental For though leukemia is not a particularly common disease, it must now and then happen that two or more cases occur in a family without there being any correlation between them. Still, the observations of familial leukemia are sufficiently many to make it likely that hereditary factors may be of etiologic significance for the development of the disease.

2 STUDY ON FAMILIAL LEUKEMIA

a *Familial Incidence.*

In order to study the frequency of familial leukemia and, if possible, arrive at a conclusion as to whether hereditary

2.—Age, 58 years Swelling of lymph nodes in the neck, the liver palpable a hand's breadth below the costal margin. White cells 32,000 to 150,000 per cmm. (lymphocytes 50 to 60 per cent). Necropsy confirmed the diagnosis

3.—At the age of 62 years large hilar lymphomas, white cells 40,000 per cmm (lymphocytes 80 per cent); gradually considerable enlargement of the spleen and universal enlargement of the lymph nodes. White cells 60,000 per cmm. (lymphocytes 97 per cent) Observed for five years The necropsy confirmed the diagnosis.

II.—Chronic myelogenous leukemia in a man (1) and his son (2).

1.—Age, 63 years. Great enlargement of the spleen. White cells 156,000 per cmm (myeloblasts 2 2 per cent, myelocytes 22 per cent, metamyelocytes 6 4 per cent, segmented neutrophils 56 4 per cent, eosinophils 1 8 per cent, basophils 6 4 per cent)

2—At the age of 25 years subleukemic leukemia with infiltrations in the skin; toward the end white cell count 37,400 per cmm, with 27 per cent of myeloblasts

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We thus know from the literature twenty-six apparently incontrovertible instances of familial occurrence of leukemia. These are in the following section discussed in connexion with the cases observed by myself Several of the authors named have discussed whether the occurrence of several cases in the same family was an expression for a causal relation between them. Since leukemia sometimes resembles an infectious disease, it has been suggested that its familial occurrence might be due to the members of a family in which a case developed being particularly exposed to infection A weighty argument against this theory is, however, that in many cases the affected individuals, though related, had not for many years, if ever, been in personal touch with each other; and, moreover, the concept of leukemia as an infectious disease must be considered as abandoned.

get P = 0.12 ‰; which shows that the incidence of leukemia is significally higher in the patient material than in the control material.

By the further investigation of the leukemia probands it was found that a few of the seventeen in whose families there were other cases of the disease were related, so that the probands mentioned represented only 14 different pedigrees (nos. 1-14). As one of these has already before been published by *Hogrelle* (1945), I am thus able to add 13 leukemia families to the 26 hitherto known.

b. Mode of *Inheritance.*

As familial leukemia is so comparatively rare, it is not possible on the basis of the existing material to calculate the risk for the different categories of relatives of getting the disease, and thus to say anything with certainty about its mode of inheritance In order, however, to shed some light on the problem, I have in Fig 3 set up the twenty-six instances known from the literature together with my own thirteen: 39 families in all, with a total of 86 cases of leukemia. The Figure shows the sex and relationship of the patients, their age at the time when the disease was recognised and the type of their leukemia

In 33 of the families there were only two cases of the disease, in 4 three, in 2 four. As the Figure further shows, there was in 17 families only leukemia in one generation, in 16 in two successive generations, in 4 in two generations, but with a leukemia-free generation between Only in 2 families did the disease appear in three successive generations. In 17 cases the patients were two sibs, in two families there was leukemia concordantly in enzygotic twins (so far as known, leukemia in one of a pair of enzygotic twins has only been reported once, by Kellett), in one family there were three sibs with the disease In 11 families in which one or several sibs had developed leukemia, the disease was present also in the father or mother; but there are still more instances in which the parents

factors play a rôle for the development of the disease in man. As said, I have tried to trace how many cases of leukemia had occurred among the relatives of the 209 patients. Nineteen could tell of at least one other case in their family, and of these statements seventeen could be verified, while in one case the hospital record could not be found (the death certificate had been issued in 1902 by a "lay coroner") and in another the patient had died in the U. S. A. and a copy of the hospital record could not be obtained.

The incidence of familial leukemia is thus in the present material at least $\frac{17 \times 100}{209} = 8.1$ per cent, or of the same order of magnitude as the familial incidence of pernicious anemia. It is true that the rate of familial incidence of the latter disease is by *Schemm* (1940) stated to be 18 7 per cent, but his material is small; by *Werner* (1938) and *Stamos* (1940) it is on the basis of much larger materials found to be, by the first 9, by the second 7 per cent. The incidence rate of familial leukemia is probably higher than 8 per cent. Not only are the two non-verified cases perhaps authentic, but especially in earlier days many children died without the cause of death being fully ascertained, and among them there may have been a few whose death was due to leukemia Lymphosarcoma must undoubtedly be considered as a type of lymphogenous leukemia; therefore the pedigree no. 175, where a paternal aunt of the proband, who herself died of stem-cell leukemia, had lymphosarcoma, may with full right be considered as an instance of familial leukemia, and when this case is included the familial incidence rate may be calculated to be 8.6 per cent.

In the families of the control material, there was only one case of leukemia. This, when compared with the seventeen cases in the families of the leukemia probands is in itself a proof of correlation between the familially occurring cases of the disease.

For the sake of completeness it may be added that with Yates' correction (*Fisher*, par. 21.01) we find $\chi^2 = 12.40$, $f = 1$, $P < 1/2$ ‰ By the exact method (*Fisher*, par. 21 03) we

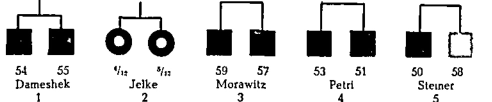
get $P = 0.12\ ^0/_{00}$; which shows that the incidence of leukemia is significantly higher in the patient material than in the control material.

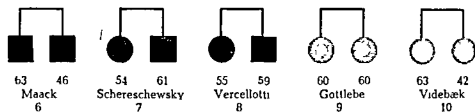
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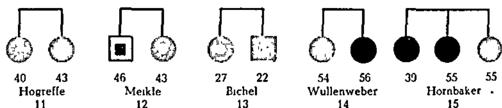
b. Mode of *Inheritance*.

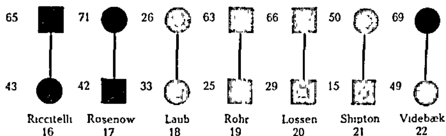
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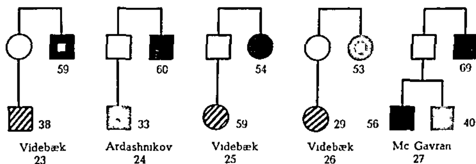
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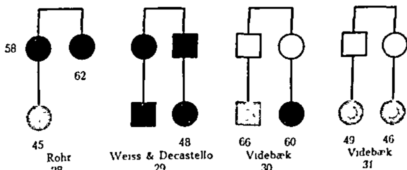

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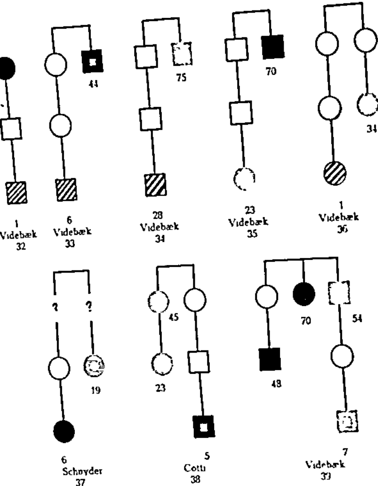

63 46
Maack
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54 61
Schereschewsky
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Vercellotti
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60 60
Gottlebe
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63 42
Videbæk
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40 43
Hogreffe
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46 43
Meikle
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Bichel
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Wullenweber
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Chronic lymphogenous Leukemia

Acute lymphogenous Leukemia

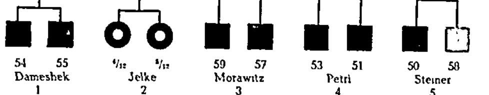
Chronic myelogenous Leukemia

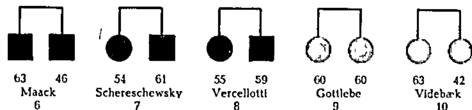
Acute myelogenous Leukemia

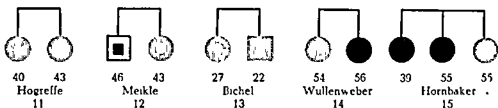
Stem-cell Leukemia

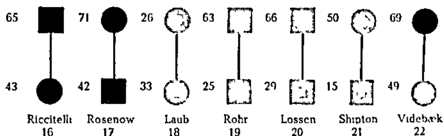
Monocytic Leukemia

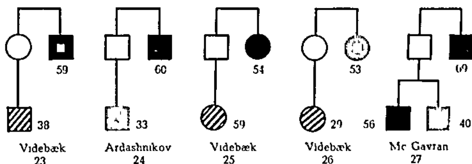
Figure 3—Schematic Representation of 39 Observations of familial Leukemia (26 from the Literature, 13 from the Author's own Material)

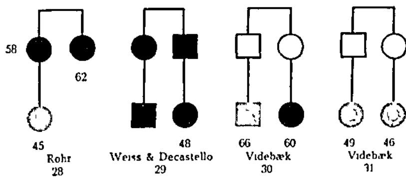

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Videbæk
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idea of hereditary factors having any rôle in the development of the disease, he nevertheless thought that the preponderance of this type among the familial cases made it probable that certain endogenous elements must be reckoned with.

From Fig. 3 it will be seen that though in many families (17) only one type occurs, there are still more (22) in which several are present. All varieties of the disease are represented, even such rare ones as monocytic and eosinophilic leukemia. Besides, there are, especially among my own observations, a number of cases designated as stem cell leukemia. In 10 families only lymphogenous leukemia is encountered, in 9 only myelogenous, in 12 both lymphogenous and myelogenous, in 1 monocytic and acute myelogenous. In 7 families we find stem cell leukemia and either lymphogenous (4 families) or myelogenous leukemia (3 families). One family, the last one depicted, is particularly remarkable by the fact that besides two cases of chronic lymphogenous there is one of chronic myelogenous and one of acute eosinophilic leukemia (in the Figure marked in as acute myelogenous). In all the families except one, in which there were more than two cases of the disease, different types were represented In summary it may be concluded that if the family tree is studied for sufficiently many generations back it may be possible not only to find leukemia in several of them, but also different types.

From Table 5, which shows, among other things, the incidence of the various types in the 86 families, it will be seen that nevertheless the lymphogenous type predominates. But it is a question if this predominance is as great as it has hitherto been claimed. If *it is true* that myelogenous leukemia is the commonest form of the disease, it is, of course, remarkable that the percentage of chronic lymphogenous cases should be nearly twice as high as that of chronic lymphogenous

In Denmark, the lymphogenous form of the chronic disease is, however, decidedly more common than the myelogenous. This appears already from an extensive survey, made in 1932 on the basis of death certificates, by *Grøn & Nielsen*, but still clearer from my own analysis (Table 6) of the incidence of the

of leukemia patients lived to an advance
signs of being similarly affected. As Fig
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patients was rather distant, but on th
incidence is demonstrated chiefly ar
individuals.

For the sake of completeness it mu
there were no consanguinous unions in
nine families.

Extrachromosomal inheritance may w
excluded, since leukemia is not consid
disease and occurs under extremely vari
cases occurring in the pedigrees of the
often found on the paternal side as on
be supposed that the inheritance is chrom
it is evident that simple dominance an
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the transmission is due to failing domina
of the dominant gene to manifest itself i
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lieved to be oftenest determined by a sin
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ance should thus be the most likely mode
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reasonable to suppose that what is inhe
to the disease; but whether this is due t
several (polymeria) must for the pres
question. (See also Chapter V, section 3).

c. *Is Leukemia a genetic Entity?*

Several authors have called attention

TABLE 6

Showing the Incidence of the different Varieties of Leukemia among 310 non-selected Patients.

Type of Leukemia	Males	Females	Total
Chronic lymphogenous	74 (46 %)	53 (35 %)	127 (41 %)
Chronic myelogenous	33 (21 %)	46 (30 %)	79 (25 %)
Acute	53 (33 %)	49 (33 %)	102 (33 %)
Monocytic	—	2 (1 %)	2 (1 %)
Total	160 (100 %)	150 (99 %)	310 (100 %)

of a fairly large number of non-selected patients. It is true that the 66 familial cases are collected from different countries and represent a period of twenty-five years, and therefore cannot be directly compared with a Danish material from the last ten years; still, it will hardly be possible to find a better parallel, seing that the 310 Danish cases were admitted to the Copenhagen hospitals from an area where nearly all leukemia patients sooner or later come under hospital treatment and thus were thoroughly examined at a time when the diagnosis of the disease had become much surer than in the past. Moreover, the diagnosis has in each single case been verified by myself

The good accordance between the relative frequency of the occurrence of the various types of the disease in familial leukemia and among a large material of non-related patients, besides the fact that nothing points to the occurrence of leukemia in the individual family being definitely confined to some particular type may be taken as evidence that no type is more particularly subject to hereditary control than others. This agrees with the observations made on inbred strains of mice, in which, though acute leukemia dominates, both chronic myelogenous and chronic lymphogenous leukemia occur. We may therefore conclude that the hereditary factors susceptible of operating in the etiology of leukemia are common, or the same, for all the different varieties of the disease.

TABLE 5
Showing the actual and relative Incidence of the different Varieties of Leukemia among the 86 Cases observed in 39 Families represented in Fig 3

Type of Leukemia	Males	Females	Total
Chronic lymphogenous .	20 (49 %)	17 (38 %)	37 (43 %)
Chronic myelogenous .	9 (22 %)	12 (27 %)	21 (24 %)
Acute	11 (27 %)	16 (36 %)	27 (31 %)
Monocytic	1 (2 %)	0	1 (1 %)
Total	41 (100 %)	45 (101 %)	86 (99 %)

various types of leukemia among 310 non-selected patients hospitalised in Copenhagen. That the myelogenous type was formerly believed to be the most frequent is probably because it is most common in younger individuals and the symptoms more marked, whereas the lymphogenous has a more torpid course and mostly occurs at an advanced age. It is therefore readily understandable that the relatively higher incidence of the latter type has not been realised until recent years, when far more cases are admitted to hospitals and the interest in the illnesses of old people is greater, partly owing to better social care for the aged

The higher incidence of the chronic lymphogenous form of the disease than the myelogenous is not a special Danish phenomenon, however. Thus, *Kirshbaum* & *Preuss* (1943) found in the record of 14,400 consecutive necropsies 26 cases of chronic lymphogenous and 20 cases of chronic myelogenous leukemia *Bethell* (1943) found 216 cases (= 43.6 per cent) of lymphogenous leukemia (including lymphosarcoma) and 175 cases (= 35.4 per cent) of myelogenous. *Haden* (1944) in an analysis of 357 cases of leukemia found 90 of the chronic myelogenous type and 101 of the chronic lymphogenous.

A comparison between Tables 5 and 6 clearly shows that the distribution of the different varieties of leukemia is precisely the same whether the question is of familial cases or

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d. *Sex Ratio.*

Tables 5 and 6 further show that the sex ratio in each of the different leukemia types is about the same in the two materials tabulated for comparison, with the only exception that there among the familial seems to be noticeably many females with acute leukemia. This difference is not significant, however. Application of the χ^2 test gives the following results:

Chronic lymphogenous leukemia ..	$\chi^2 = 0.49$, $f = 1$; $50\% > P > 30\%$
" myelogenous " ..	$\chi^2 = 0.11$; $f = 1$; $80\% > P > 70\%$
Acute leukemia	$\chi^2 = 1.07$; $f = 1$; $50\% > P > 30\%$
Leukemia as a whole	$\chi^2 = 0.42$; $f = 1$; $70\% > P > 50\%$

In 11 of the families with only two cases of the disease, only males were affected, in 10 only females, in 12 both a male and a female. As leukemia occurs with practically the same frequency in the two sexes, the ratio for the three possible combinations male + male, female + female and male + female would, by a fortuitous combination, be as 1:1·2. Among the thirty-three families of which there is question here, we should thus expect to find 8 (1/4) with two male cases, 8 (1/4) with two female, and 16 (1/2) with a male and a female case, whereas the actual figures are respectively 11, 10 and 12. The deviation is not significant, however ($\chi^2 = 1.27$; $f = 2$; $30\% > P > 20\%$) Sex-limitation can thus be excluded, and sex-linked inheritance has not been demonstrated.

e. *Age Incidence.*

In 83 of the 86 cases, the patient's age at the onset of the disease is known. The average age for these, with exception of the patients with monocytic leukemia, is shown, compared with the age incidence in a non-selected leukemia material, in Table 7 and Fig. 4. Table 7 shows that in all the varieties listed the average age is lower for the familial cases than for the non-selected patients, and also that lymphogenous leukemia,—the largest of the groups,—has its highest incidence at an earlier age in the familial cases. Thus, for leukemia as a whole, not

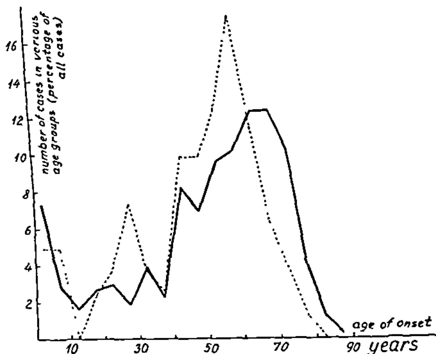


Figure 4 —Distribution by Age of 82 familial Cases of Leukemia (.) and 310 non-selected Patients with Leukemia (———) The Number of Cases in each of the 5-year Groups is expressed in Percentage of the total Number of Cases

only the age of the maximum incidence but also the average age is lower in the familial cases, in other words, familial leukemia seems to manifest itself earlier than is usually the case with the disease.

Fig 4 shows the distribution by age of the 82 familial cases and of 310 non-selected The shift to the left, of the familial cases, seems to apply only to the right part of the curve, which represents mainly cases of chronic leukemia The same distribution by age is in Fig 5 represented in a probits diagram which shows a shift to the left for those of the familial cases that occur after about the thirtieth year of life; which is to say that they manifest themselves earlier than normal

a. *Sex Ratio.*

Tables 5 and 6 further show that the sex ratio in each of the different leukemia types is about the same in the two materials tabulated for comparison, with the only exception that there among the familial seems to be noticeably many females with acute leukemia. This difference is not significant, however. Application of the χ^2 test gives the following results:

Chronic lymphogenous leukemia ..	$\chi^2 = 0.49$; $f = 1$; $50\% > P > 30\%$
„ myelogenous „ ..	$\chi^2 = 0.11$; $f = 1$; $80\% > P > 70\%$
Acute leukemia	$\chi^2 = 1.07$; $f = 1$; $50\% > P > 30\%$
Leukemia as a whole	$\chi^2 = 0.42$, $f = 1$, $70\% > P > 50\%$

In 11 of the families with only two cases of the disease, only males were affected, in 10 only females, in 12 both a male and a female. As leukemia occurs with practically the same frequency in the two sexes, the ratio for the three possible combinations male + male, female + female and male + female would, by a fortuitous combination, be as 1·1:2. Among the thirty-three families of which there is question here, we should thus expect to find 8 (1/4) with two male cases, 8 (1/4) with two female, and 16 (1/2) with a male and a female case, whereas the actual figures are respectively 11, 10 and 12. The deviation is not significant, however ($\chi^2 = 1.27$; $f = 2$; $30\% > P > 20\%$). Sex-limitation can thus be excluded, and sex-linked inheritance has not been demonstrated.

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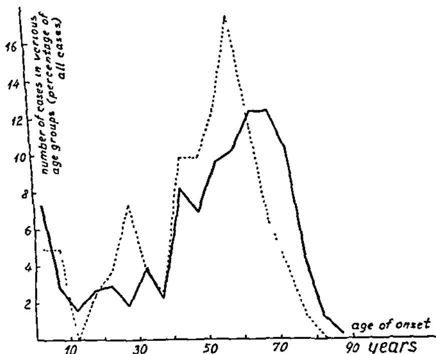


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99
95
90
80
50
20
10
5
1
05
per cent of cases
82 familial cases
310 non-selected cases
Leukemia (all types)
10 20 30 40 50 60 70 80 90

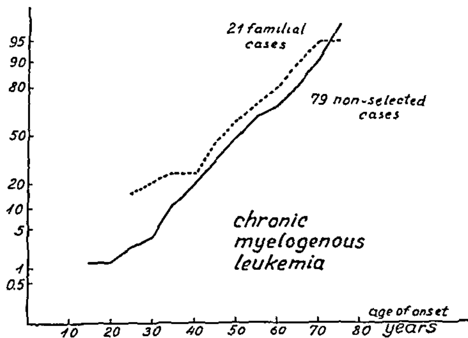


Figure 5 —Probits Diagrams showing the Distribution by Age of familial Cases of Leukemia ( ) and the normal Age Distribution for the corresponding Type of the Disease

82 familial cases

310 non-selected cases

per cent of cases

99 95 90 80 50 20 10 5 1 05

Leukemia (all types)

10 20 30 40 50 60 70 80 90

21 familial cases

79 non-selected cases

95 90 80 50 20 10 5 1 05

chronic myelogenous leukemia

age of onset

10 20 30 40 50 60 70 80 years

Figure 5—Probits Diagrams showing the Distribution by Age of familial Cases of Leukemia (-) and the normal Age Distribution for the corresponding Type of the Disease

TABLE 7.
Showing the average Age of the different Varieties of Leukemia in 82 familial and 308 non-selected Cases

Type of Leukemia	Familial			Non-selected		
	No of cases	Age of maximum incidence	Average age	No of cases	Age of maximum incidence	Average age
Chr. lymphogen. Males ..	18	55—59	56.6	74	65—69	59.2
Females	16	55—59	53 6	53	70—74	62 4
Chr. myelogen. Males .	9		48.4	33	40—49	50 9
Females	12	40—49	43 0	46	40—49	50.2
Acute lymphogenous ..	5		21.7	30	0— 9	35.9
Acute myelogenous ...	15		38.9	27	60—69	42 4
Stem-cell	7		23.1	45	0— 4	24.7
All cases	82	55—59	44.9	308	60—70	48.9

If we apply the χ^2 test to the two age distributions, we find for leukemia as a whole no significant shift to the left of the familial cases ($\chi^2 = 13.88$; $f = 8$, $10\% > P > 5\%$), but a comparison between the 34 familial cases of chronic lymphogenous leukemia with the 127 non-selected cases of the same type shows an indubitable shift to the left ($\chi^2 = 11.87$; $f = 4$; $2\% > P > 1\%$). The corresponding figures for chronic myelogenous leukemia are: $\chi^2 = 3.89$, $f = 2$; $20\% > P > 10\%$; which shows that there is no significant shift to the left of the familial cases of this group. That a tendency to such a shift exists is evident, however, from Table 7, as also from the probits diagram Fig. 5, where the whole curve for the familial cases is shifted to the left in relation to the curve for 79 non-selected cases of the same type of leukemia It is probable that a larger material would show a significant difference.

The group: acute leukemia is, as said, rather heterogeneous and the different types composing it represented by rather small figures. In all of them, the average age for the familial cases is lower, however, than for the non-familial cases (Table 7), and it would thus seem that also acute leukemia manifests itself earlier in the cases where the disease is familial. The probits diagram of the acute cases shows in the higher age

classes a distinct shift to the left for the familial cases. That a similar shift is not seen in the younger age classes may perhaps be because a certain hereditary taint is less likely to provoke the onset of the disease in a young individual than in an older one, in whom, alone by reason of his longer span of life, the different non-hereditary accelerating factors have reached a greater intensity.

All that has been said above thus leads to the conclusion that chronic lymphogenous leukemia in familial cases manifests itself earlier in life than it is otherwise usual with this disease, and the same seems to be the case, though not statistically certain, as regards both chronic myelogenous and acute leukemia.

The figures in Fig. 3 seem to show that leukemia in sibs very often occurs at about the same age in both. As a correlation between the ages at which they get the disease must show itself by the standard deviation for the ages at which the disease is recognised being less in the case of the individual pairs of sibs than from one family to another, the existence of a correlation with regard to age can be demonstrated by determining the ratio between these two standard deviations. I have made such a calculation on the basis of the observations on sibs represented in Fig 3 (with omission of the two pairs of enzygotic twins).

For the square of the standard deviation for the average ages in different families we get $s_1^2 = 167.33$, for the square of the standard deviation for the ages of sibs in the same family $s_2^2 = 56.02$ By applying Fisher's z test (*Fisher*, chapter VII) we find $e^{2z} = \frac{s_1^2}{s_2^2} = 2.99$, and since the degrees of freedom are respectively 15 and 17, we get for the 2.5 per cent point $e^{2z} = 2.72$, for the 1 per cent point $e^{2z} = 3.31$. The value found for e^{2z} therefore corresponds to $P = 1.8\,\%$, which is to say that the age correlation observed is significant That the leukemia in sibs thus occurs at about the same age in both of them makes

it unlikely that its occurrence should be a mere matter of fortuitous coincidence, and supports the supposition of a genetic relation between the cases.

In order to examine if there is a similar correlation between the ages of related leukemia patients belonging to different generations, I have calculated the correlation coefficient and used Fisher's Tables to estimate if the values found are significant. From Table 8 it will be seen that this is the case only as regards the categories uncles and aunts, nephews and

TABLE 8
Showing the calculated Correlation between the Ages of related Leukemia Patients in the Families represented in Fig. 3

Categories of relatives compared with the last-born leukemia patient	No of the family in Fig 3	Correlation coefficient r	Number of degrees of freedom f	P
Parents.	16—22, 28, 29, 38	0 4252	7	$P > 10\%$
Uncle or Aunt.	23—28, 36—39	0 8317	8	$1\% > P > 1‰$
Grandparents or their Brothers or Sisters....	32—35, 38, 39	0 8080	4	$10\% > P > 5\%$

nieces. That all the values found are positive means that a higher, resp. lower, age of manifestation of the leukemia in one of the patients oftenest coincides with a higher, resp lower, age of manifestation in the other. There thus seems to be an age correlation also between more distantly related leukemia patients.

As the figures in Fig. 3 seem to indicate that the age at which the leukemia manifests itself is lower in one generation than in the foregoing, I have calculated the average difference between the ages of the related patients, and have by means of Student's t test (*Fisher, par. 24*) found a *significant deviation* from zero, as shown in Table 9.

While the difference in age between leukemia patients of successive generations is about twenty years, we see that it is about twice as great when there is a leukemia-free generation

TABLE 9

Showing the calculated average Difference in Age between Leukemia Patients belonging to different Generations of the Families represented in Fig 3.

Categories of relatives compared with the last born leukemia patient	No. of the family in Fig 3	Average difference in age (years)	t	Number of degr of freedom f	P
Parents	16-22, 28, 38	23.2	4.92	8	$1\% > P > 1‰$
Uncle or Aunt	23-28, 36-39	18.3	5.69	9	$1‰ > P$
Grandparents or their Brothers or Sisters	32-35, 38, 39	47 3	16 47	5	$1‰ > P$

between them. Though this lends support to the view that the *disease manifests* itself particularly early when a *hereditary* taint has been demonstrated, the cause of this greater difference may be that there among the brothers and sisters of the parents and grandparents have been some whose leukemia was *never recognised* because they died so young and so long ago that the cases were not diagnosed as such

3 CONCLUSION

The investigation here described shows that the occurrence of several cases of *leukemia in the same family* is much too frequent to be explained as a coincidence, and that the familial incidence, which amounts to at least 8 per cent of all cases, *is therefore* an expression for a relation between the cases in question. *Since the demonstrated* relation between them cannot be reasonably explained in any other way, it must be supposed to be genetic Though the present material is too small to warrant any statistical calculation of the risk of getting leukemia, *simple dominance and* recessivity can be excluded, but there is a possibility of failing dominance or polymeria. Sex-limitation is excluded, and sex-linked inheritance has *not* been demonstrated. There is no doubt that chronic lympho-

genous leukemia manifests itself earlier in the familial cases than is otherwise the case. Familial cases of chronic myelogenous leukemia and acute leukemia have a tendency to early manifestation. Leukemia in sibs oftenest shows itself at about the same age in both, and also between more distantly related leukemia patients there seems to be a correlation in this respect. Genetically, leukemia appears to be an entity, since the incidence of the various types among the familial cases corresponds exactly to their relative frequency among the non-familial cases, and since the cases of leukemia that occur within an individual family do not have any definite type of election. The gene, or genes, which have a rôle in the production of leukemia are evidently not specific as regards the type of the disease.

Chapter III

GENETIC RELATION BETWEEN LEUKEMIA AND OTHER BLOOD DISORDERS

The fact that leukemia and other disorders of the blood-forming organs have not infrequently been found in the same family has suggested that there should exist not only a, with regard to the type of the condition, homologous disposition to blood disorder, but also a heterologous

I FAMILIAL LYMPHOCYTOSIS AND LYMPHOGENOUS LEUKEMIA

It was first pointed out by *Deutsch* (1932), and seemed to be confirmed by *Winkler* (1939) among others, that lymphocytosis is often found in near relatives of patients with lymphogenous leukemia, and that these relatives represent "des formes frustes" of this disease (*Ardashnikov*, 1937), similarly to what has been asserted about the so-called "status lymphaticus" (*Arnsperger*, 1905) The basis for this assertion seems very slight, however Not only is it questionable if the lymphocytosis observed was real, and, moreover, the investigations were few and carried out in haphazard fashion; but the conception of the status lymphaticus has changed so greatly, and has been the subject of so much discussion, that we may be justified in not considering this ill-defined condition in relation to lymphogenous leukemia As publications by *Deutsch* (1932),

Mohr (1938) and *Cicovacki* (1940) are still being referred to, however, by other writers on the subject, I shall briefly mention them here.

Deutsch examined forty-one relatives of thirteen children with lymphogenous leukemia and twenty-five relatives of seven children with "lymphatische Reaktion", and states that they nearly all showed lymphocytosis up to as high as 70 per cent. As the high values were, however, found only in children, it is a question if the condition was really pathologic. Besides, *Deutsch* only gives the lymphocyte percentages, and about the white cell counts merely says that they showed about normal values. The presence of lymphocytosis cannot however be proved on the basis of the lymphocyte percentage alone; therefore no importance can be attached to his results.

Mohr's investigations are very few, and his figures only percentage values. Several other workers, among them *Wullenweber* (1937) and *Gottlebe* (1938) have stated that they found increased lymphocyte percentages in some relatives of patients with lymphogenous leukemia; but they, too, give only the percentage figures, not the total white cell count.

Cicovacki reported that he in thirteen out of nineteen relatives of eight patients with lymphogenous leukemia had found evident lymphocytosis of from 34 to 50 per cent. Closer scrutiny of his figures shows, however, that the white cell count was only increased in one case, in which it was 12,800 per cmm. But the lymphocytes are stated to have formed 29 per cent of this total, which is to say that they were 3,700 per cmm., which does not exceed the limit for a normal lymphocyte count. His highest lymphocyte percentage, 50 per cent, was found with a white cell count of 4,500 per cmm., and this is nothing extraordinary, being only a question of relative, not of absolute lymphocytosis Absolute lymphocytosis cannot be demonstrated in any of the thirteen cases, since the absolute lymphocyte figures varied from 1,275 to 4,200

None of the published investigations concerning lymphocytosis in relatives of patients with leukemia are convincing as supports for the theory of a familial, latent form of lympho-

genous leukemia. Therefore, the works cited above cannot be used in the discussion of whether a genetic factor operates in the production of the disease.

2 LEUKEMIA AND PERNICIOUS ANEMIA IN THE SAME FAMILY AND IN THE SAME PATIENT

a. *Literature.*

The first observation of pernicious anemia and leukemia in the same family is probably the one reported by *Schumann* (1925), who recorded a case of a patient with pernicious anemia whose daughter died of chronic myelogenous leukemia. *Koehler* (1928) reported, without comments, that a sister of a patient with a well diagnosed chronic myelogenous leukemia had pernicious anemia *Strandell* & *Lemming* (1931) observed two brothers, one of whom had pernicious anemia, the other chronic myelogenous leukemia. *Strandell* (1936) recorded a case of a woman with pernicious anemia, whose daughter had acute myelogenous leukemia, and a case of pernicious anemia in a woman whose brother died of "leukemia lienalis". Of the last two cases he believed, however, that their occurrence in sister and brother was simply incidental, and that there was no genetic relation between them. *Ardashnikov* (1937) studied the pedigrees of 33 patients with leukemia and found no cases of pernicious anemia in any of them He mentions, however, that *Presnyakov* in a study of relatives of 100 patients with pernicious anemia among 528 of these who were over twenty years old found 3 cases of pernicious anemia and none of leukemia The value of *Presnyakov's* investigation is considerably lessened, though, by the fact that the number of relatives is rather small, on the average 5 to 6 for each of the 100 probands. This is probably the reason why he only found pernicious anemia in the families of three of them,—a familial incidence considerably lower than recorded by other observers. Werner (1938), for instance, found in an investigation of 525 relatives of 57 probands a familial incidence of 9 per cent, and *Stamos*

5*

(1940) among 645 cases a familial incidence of 7.9 per cent. It may therefore be supposed that also *Presnyakov*, if his investigation had extended to a wider range of relatives, would have found more cases of pernicious anemia, and perhaps also a few cases of leukemia. At any rate, his results do not negative the theory of a genetic relationship between the two diseases. Though *Werner* does not mention the possibility of such a relationship, it is nevertheless remarkable that he among the relatives of his 57 probands found not less than 4 cases of leukemia.

We thus know from the literature 9 instances of leukemia and pernicious anemia occurring in the same family. In 4 of them the leukemia was chronic myelogenous, in 1 acute myelogenous, in the four others the type is not known.

In connexion with the question of a possible relationship between pernicious anemia and leukemia (perhaps specially myelogenous leukemia), the transition of the former condition into the latter is of particular interest. The first case of this kind was described by *von Leube* (1900); since then several cases of this so-called leukanemia have been recorded by other authors. As we now know that there are a great many perniciosiform anemias, the presence of megaloblastic bone marrow and gastric achylia, together with reticulocytic reaction to specific treatment, must be considered as essential criteria for the diagnosis of pernicious anemia. In fact, very few of the reported cases of pernicious anemia and leukemia in the same individual meet these requirements; with exception, of course, of those where the pernicious anemia had developed as result of extensive leukemic infiltration in the gastric mucosa, as described by *Touw & Graafland* (1939) among others. In these the special localisation of the leukemia sufficiently explains the development of the anemia. Indubitable cases have, however, been recorded by several observers, for instance in 1936 by *Rich & Schill* (lymphogenous leukemia), in 1941 by *Sterne, Schiro & Molle* (myelogenous leukemia) and *Schulz* (myeloblastic leukemia), in 1944 by *Wolley* (myelogenous leukemia). All these authors believe, however, that the association

of the two diseases in the same individual was incidental; while *Bethell* and his co-workers (1945) think that the association is due to constitutional factors.

b. *Author's Investigations.*

As it has been generally accepted that hereditary factors may play a rôle for the development of pernicious anemia, and as I now also know that hereditary factors may operate in the production of leukemia, it will be of particular interest to demonstrate a genetic relation between the two diseases, showing itself in an excess incidence of pernicious anemia in the families of patients with leukemia. On the basis of the sparse information I have been able to gather from the literature, all I can say is that leukemia and pernicious anemia are sometimes found in the same family, and also sometimes in the same patient. Thus, it does not seem impossible that there may be a genetic relationship between the two diseases. The reason why the observations of them in the same family are so few may simply be that such a combination has not been paid sufficient attention to To get some more light on the subject it will be necessary, however, to examine how often pernicious anemia occurs among relatives of patients with leukemia

On examination of the 310 leukemia patients it was found that 2 of them also had pernicious anemia of several years standing before the leukemia was diagnosed

One of them was the female proband for pedigree no 105 She got pernicious anemia at the age of 38 years (hyperchromic, megalocytic anemia, gastric achylia, leukopenia, thrombopenia, increased basal metabolism, paresthesias, good effect of specific treatment), six years later she got chronic myelogenous leukemia, the diagnosis of which was verified by necropsy

The other case does not belong to the proband material The patient was a man, who at the age of 40 years got paresthesias in the tongue and five years later his gait became unsteady A year afterwards he was found to be suffering from pernicious anemia Specific treatment resulted in considerable improvement, but five years later there came considerable enlargement of the lymph nodes and spleen, the white cell count

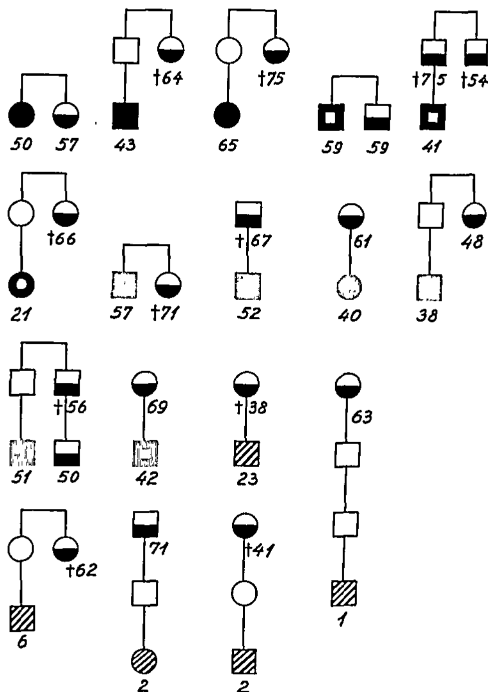


Figure 6.—Author's Observations of Leukemia and pernicious Anemia in the same Families (For Key to the Symbols see Fig 3).

rose to 156,000 per cmm, nearly all lymphocytes Six months later the white cell count was 310,000 with 98 per cent of lymphocytes

That pernicious anemia thus may precede both acute and chronic, lymphogenous and myelogenous leukemia seems to point to a relation between these otherwise very dissimilar conditions

The investigation of the pedigrees of the 209 leukemia probands showed verified cases of pernicious anemia in 17 of them (nos. 36, 63, 70, 88, 92, 94, 116, 119, 134, 137, 141, 159, 180, 190, 199, 201 and 203), that is in 8 per cent of the families. In two of them there was more than one case; namely, in no. 94 in a father and his son, in no. 137 in two brothers. In the control material, pernicious anemia was found only in 6 of the 200 families, that is in 3 per cent; in one of these there were 2 cases, in two brothers. The incidence of pernicious anemia among the relatives of the patients with leukemia is thus remarkably high; a conclusion which is also borne out by statistical examination, for by applying the χ^2 test with Yates's correction to the number of tainted families in the patient- and control materials we get $\chi^2 = 4.15$, $f = 1$, $5\,\% > P > 2\,\%$, or, by exact treatment (see *Fisher*, par. 20 02) P = 3.06.

There is thus an indubitable relation between leukemia and pernicious anemia According to the literature, this relation should exist particularly between the anemia and chronic lymphogenous leukemia, but as it will be seen from Fig 6, pernicious anemia occurs in the present material in familial association both with chronic lymphogenous (3 families), acute lymphogenous (3 families), chronic myelogenous (5 families), acute myelogenous (1 family) and stem-cell leukemia (5 families), and is thus in different families associated with nearly every type of leukemia, in this material oftenest with the acute form (9 families), most rarely with the chronic lymphogenous form of the disease The material is rather small, however, and there is no particular preponderance of myelogenous leukemia.

As Fig 6 shows, the patients with pernicious anemia belong in all the families to an older generation than the leukemia

cancer which becomes the outstanding feature of the general picture.

3 LEUKEMIA AND OTHER BLOOD DISEASES IN THE SAME FAMILY

a. *Literature.*

Also other blood diseases than pernicious anemia have now and then, though rarely, been observed in the families of patients with leukemia. *Ardoshnikov* (1937) found in 31 families of leukemia patients no other blood diseases than leukemia. *Wolff* (1931) found agranulocytosis in the brother of a woman with acute leukemia. *Petri* (1933) found hypochromic iron deficiency anemia in a cousin of two brothers with leukemia. *Hirschfeld* (1935) and *Cotti* (1941) have briefly mentioned observations of Hodgkin's disease and leukemia in the same family, *Seiler* (1935) found acute leukemia in a child whose maternal granduncle was a hemophiliac. *Holse* (cit. by Gansslen) found polycytemia vera and leukemia in one family.

b. *Author's Investigations.*

The published observations of leukemia and other blood diseases are thus few, for the most part collected at random and at any rate quite insufficient as proof of a heterologous disposition to blood disease or of a relation between different diseases of the blood-forming organs On the other hand, the possibility of a certain common constitutional basis cannot, of course, be excluded, but a closer approach to the solution of the problem will require a more systematic study of the occurrence of the different blood diseases in relatives of a larger number of patients with leukemia as well as the ascertainment of the frequency with which they occur in the families of sound individuals

From the persons composing the present patient- and control material I tried to get information about the occurrence of such

patients. One reason for this is that whereas leukemia may occur at any age, pernicious anemia rarely develops before the thirtieth year of life. If we therefore leave out of account the families in which the leukemia patients developed the disease before the age of thirty, there is still in those families in which there was leukemia and pernicious anemia in different generations a significant age difference, between the patients with the two diseases, of 19.8 years. By applying Student's t test (Fisher, par. 24) we find $t = 5.08$, $f = 8$, $P < 1$ ‰. Though the pernicious anemia in some of the cases was not diagnosed until shortly before death and may thus very possibly have been present for a number of years, an average age difference of about 20 years suggests a relation between the two diseases.

It is not possible to say anything certain about the nature of the relation between pernicious anemia and leukemia, but it lies near to conceive it as due to a hereditary factor of importance for the functioning of the hemopoietic tissue, perhaps for its capacity for differentiation, favoring the development now of leukemia, now of pernicious anemia. The relationship may perhaps be due to a hereditary disposition which leukemia and pernicious anemia have in common with cancer. Whatever the explanation may be, it is noticeable that pernicious anemia has often been found associated with cancer of the stomach (*Thiele*, 1938, and *Schulten*, 1943, among others), and that there in the families of leukemia patients can be demonstrated a high incidence of leukemia, pernicious anemia and cancer (see Chapter V). An investigation of the occurrence of the three diseases among the relatives of patients with pernicious anemia might perhaps solve this problem. It is highly probable that stomach cancer, especially, is frequent among these relatives, but it must be remembered that the diagnosis of that particular form of cancer has often been made wrong use of. Moreover, it is probably the most frequent form of cancer, and if the incidence of cancer as a whole is high among relatives of patients with pernicious anemia it will therefore also be stomach

There are thus in the patient material some diseases which have their replica in the control material, and others of which it cannot be said with certainty whether they were leukemia or pernicious anemia. The conclusion of the investigation as a whole must be that the incidence of blood diseases in the families of the leukemia probands is not abnormally high. A genetic relation between leukemia and other diseases of the blood-forming organs,—with exception of pernicious anemia,—can not be demonstrated.

diseases in their families, and found, of course, in both materials a number of cases of various types.

Thus, the brother of a leukemia proband (Pedigree no. 68) had Hodgkin's disease, and the same was the case with the father of one of the control probands. A nephew of another leukemia proband (Pedigree no. 24) had hemophilia, but as also the niece of one of the control probands was a hemophiliac the familial occurrence of hemophilia and leukemia can only be considered as a coincidence. In the patient material were found a few cases of blood disease, some of them ill-defined, to which there were no corresponding in the control material. A sister of the proband for pedigree no. 18 died with symptoms of hemorrhagic diathesis and splenomegaly (possibly a case of leukemia), a sister of the proband for pedigree no. 43 died of an atypical macrocytic, not pernicious anemia; a maternal aunt of the proband for pedigree no. 115 died after being ill for a year with chronic, probably pernicious anemia. The family no. 116 is particularly interesting by the fact that the proband's mother suffered from pernicious anemia and her father's sister was under treatment for polycytemia vera. In the family no. 147, a sister of the proband's mother died young of agranulocytosis. In the family no. 91, three sibs had anemia, but of particular pathogeny: one died of erythroblastosis fetalis, the second was being treated for the same disease, the third had a rather severe iron deficiency anemia. In family the no. 14, two girls, respectively 15 and 7 years old, had died owing to hemorrhagic diathesis. None of them had been hospitalised, and as their deaths occurred at a time when the possibility of leukemia had hardly been considered (1895 and 1898) it may very likely have been cases of that disease. At all events it is highly probable that their condition was due to hereditary disposition, since the family as a whole presented an exceedingly pathologic picture. In the same sibship to which the two girls already mentioned belonged there were, besides, 4 cases of cancer and 1 of leukemia; a sister and a brother of the mother had died of leukemia, another sister of the mother, and the mother's father, had died of cancer.

There are thus in the patient material some diseases which have their replica in the control material, and others of which it cannot be said with certainty whether they were leukemia or pernicious anemia. The conclusion of the investigation as a whole must be that the incidence of blood diseases in the families of the leukemia probands is not abnormally high. A genetic relation between leukemia and other diseases of the blood-forming organs,—with exception of pernicious anemia,—can not be demonstrated

diseases in their families, and found, of course, in both materials a number of cases of various types.

Thus, the brother of a leukemia proband (Pedigree no. 68) had Hodgkin's disease, and the same was the case with the father of one of the control probands. A nephew of another leukemia proband (Pedigree no. 24) had hemophilia, but as also the niece of one of the control probands was a hemophiliac the familial occurrence of hemophilia and leukemia can only be considered as a coincidence. In the patient material were found a few cases of blood disease, some of them ill-defined, to which there were no corresponding in the control material. A sister of the proband for pedigree no. 18 died with symptoms of hemorrhagic diathesis and splenomegaly (possibly a case of leukemia), a sister of the proband for pedigree no. 43 died of an atypical macrocytic, not pernicious anemia; a maternal aunt of the proband for pedigree no. 115 died after being ill for a year with chronic, probably pernicious anemia. The family no. 116 is particularly interesting by the fact that the proband's mother suffered from pernicious anemia and her father's sister was under treatment for polycytemia vera. In the family no. 147, a sister of the proband's mother died young of agranulocytosis In the family no. 91, three sibs had anemia, but of particular pathogeny: one died of erythroblastosis fetalis, the second was being treated for the same disease, the third had a rather severe iron deficiency anemia In family the no. 14, two girls, respectively 15 and 7 years old, had died owing to hemorrhagic diathesis. None of them had been hospitalised, and as their deaths occurred at a time when the possibility of leukemia had hardly been considered (1895 and 1898) it may very likely have been cases of that disease. At all events it is highly probable that their condition was due to hereditary disposition, since the family as a whole presented an exceedingly pathologic picture In the same sibship to which the two girls already mentioned belonged there were, besides, 4 cases of cancer and 1 of leukemia; a sister and a brother of the mother had died of leukemia, another sister of the mother, and the mother's father, had died of cancer.

as rare, since they only found it in 3 of 83,000 patients hospitalised during the period 1922-1940 As a rule it seemed that the diabetes had been present for some time before the leukemia developed Of 6 of the 15 cases in which the two diseases occurred in the same patient, there are necropsy records, but in none of them is there any mention of observation of leukemic infiltration in the hypophysis or in Langerhans's islands So far as it is possible to judge from the existing reports, the simultaneous presence of leukemia and diabetus mellitus in the same patient must be considered as only a coincidence.

Goldstein's (1931) finding of lymphogenous leukemia in a patient with acromegaly of twenty years' standing does not warrant any conclusion about a causal connexion between the two diseases.

The cause of the increased basal metabolic rate in leukemia, and sometimes also in pernicious anemia, polycythemia vera and Hodgkin's disease, is not clear, but has often been ascribed to hyperfunction of the thyroid gland It must be remembered, however, that though increased metabolism is an important symptom in hyperthyroidism it is not pathognomonic for the condition and is only one of the guiding points for the diagnosis Microscopic changes indicative of hyperfunction of the thyroid gland seem never to have been demonstrated in leukemia, neither does strumectomy or the administration of iodine have any consistent effect Though all reports of hyperthyroidism in leukemia must thus be received with great reservation, it is nevertheless remarkable that *Kirshbaum* & Preuss (1943) observed nodose struma and hyperthyreosis in not less than 13 of 123 patients with various forms of leukemia.

b *Author's Investigations.*

In some of the 310 leukemic *patients with whom* the present investigation started, a few dyshormonal conditions were found either in the anamnesis or at physical examination The basal metabolism was not measured consistently in all of them, but in a few it was found to be moderately increased, and on the

Chapter IV

GENETIC RELATION BETWEEN LEUKEMIA AND ENDOCRINE DISORDERS

1 DYSCRINISM IN PATIENTS WITH LEUKEMIA

a. *Literature.*

It is not to be wondered that the hormonal balance becomes disturbed when a gland of internal secretion during the course of a leukemia is invaded by leukemic cells,—which, however, is said to be rare (*Forkner*, 1938),—and that thus, for instance, diabetes insipidus occurs when the posterior lobe of the hypophysis is involved with leukemic infiltrations, as observed by *Sheldon* (1927) and *Yang* (1936), among others. It is by no means in all cases, though, that an observed disturbance of the hormonal balance can be explained as due to leukemic infiltrations in the organs.

According to *Joslin* (1935) diabetes mellitus is seldom associated with leukemia, but he observed 6 patients with diabetes, 4 of whom got lymphogenous, 1 monocytic and 1 myelogenous leukemia. The association of acute myelogenous leukemia and diabetes mellitus in the same patient has been described by *Elman & Marshall* (1936) and by *Dahl* (1946), that of chronic lymphogenous leukemia and diabetes mellitus by *Hart, Lisa & Riedel* (1939), who also mention that *Wright* (1928) observed diabetes mellitus in 3 patients with chronic myelogenous and 2 with chronic lymphogenous leukemia. *Levi & Friedman* (1941) consider the association of the two diseases

as rare, since they only found it in 3 of 83,000 patients hospitalised during the period 1922-1940 As a rule it seemed that the diabetes had been present for some time before the leukemia developed. Of 6 of the 15 cases in which the two diseases occurred in the same patient, there are necropsy records, but in none of them is there any mention of observation of leukemic infiltration in the hypophysis or in Langerhans's islands So far as it is possible to judge from the existing reports, the simultaneous presence of leukemia and diabetus mellitus in the same patient must be considered as only a coincidence.

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b *Author's Investigations.*

In some of the 310 leukemic patients with whom the present investigation started, a few dyshormonal conditions were found either in the anamnesis or at physical examination. The basal metabolism was not measured consistently in all of them, but in a few it was found to be moderately increased, and on the

whole the findings did not warrant the diagnosis of Graves' disease. Only in the anamnesis of two women (pedigrees 55 and 106),—that is in about 1 per cent of the females,—was there information about that disease, a frequency similar to that with which it normally occurs in females (in the control material in 0.5 per cent of these).

Nodose, atoxic struma was found in 3 women with respectively chronic lymphogenous, chronic myelogenous and stem-cell leukemia; that is in about 1 per cent of the patients or about 2 per cent of the females; which according to *Dalsgaard-Nielsen* (1940) and *Rosenquist* (1940) is the normal frequency.

Diabetes mellitus was found in 6 patients: 2 men and 1 woman with chronic lymphogenous, 1 man with acute lymphogenous, and 1 man and 1 woman with acute myelogenous leukemia; that is a frequency of about 2 per cent; while the frequency in the whole control material was about 1.6 per cent.

A leukemic patient (Pedigree no. *19*) presented a clinically clear case of diabetes insipidus (diuresis about 5 liters; good effect of insipidin). As he died at home, it could not be ascertained if there was leukemic infiltration of the hypophysis, but roentgen examination showed a calcareous shadow in the middle of the sella turcica which was not enlarged.

A man who at the age of fifty-three got typical chronic lymphogenous leukemia (white cells 75,800 per cmm., with 94 per cent of lymphocytes) had been chryptorchid, without secondary sexual characters, until his thirty-second year, when the conditions suddenly and spontaneously became normal.

2 DYSCRINISM AND LEUKEMIA IN THE SAME FAMILY

a. *Literature.*

Naegeli (1920) mooted the suggestion that leukemia might be due to a disharmony between the glands of internal secretion, though without attributing a determining influence in that

respect to the action—or absence—of any single hormone in particular. Many writers have identified themselves with this theory as regards the symptoms of dyscrinism sometimes observed in patients with leukemia, and have believed that it was supported by the finding of endocrine disorders in relatives of these patients Much of what has been said in this respect is, however, extremely imaginative and based only on isolated observations. *Hanzel* (1908), *Schumann* (1925) and *Scherecschewsky* (1926), among others, found a few cases of diabetes mellitus in relatives of leukemia patients, and *Maack* (1940) recorded the finding of respectively 1 and 3 cases of the same disease in the families of two patients with leukemia, and suggested the possibility of a genetic association.

Parallels between Graves' disease and leukemia have been drawn by several writers on the ground that the basal metabolism is increased in both diseases Hyperthyreosis has been observed in the families of leukemic patients by *Curschmann* (1936), *Wüllenweber* (1937) and *Maack* (1940), but none of them has ventured to draw any definite conclusions from the fact

b *Author's Investigations.*

As said in Chapter 1, I have in this investigation particularly sought for information about Graves' disease, myxedema and diabetes mellitus in the families of the leukemia probands. Among the male relatives there were no indubitable cases of Graves' disease, among the female there were 17,—that is in 0 4 per cent of all the relatives, 0 8 per cent of the female,—the same frequency which *Bartels* (1941) found for the Danish population in general (males and females: 0.4 ± 0 12 per cent). In the control material, the disease was found in 3 males and 9 females, i e. in 0 3 per cent of both sexes together, 0 5 per cent of the females Thus, my material does not show any excessive frequency of Graves' disease in the families of the leukemia patients, and since the affection is on the whole of

rather common occurrence it is not surprising that it is now and then found in relatives of these.

Myxedema was found in 8 relatives of the leukemia probands,—1 male and 7 females,—i.e. in 0.20 per cent of both sexes together, in 0.34 per cent of the females, of whom there were 2031. In the control material, the disease was only found in 5 of the 1805 females, i.e. in 0.28 per cent of these. The difference may very well be incidental, though, since the χ^2 test with Yates' correction gives $\chi^2 = 0.12$, $f = 1$, $80\% > P > 70\%$. There is thus no sure evidence of myxedema being particularly frequent among relatives of patients with leukemia.

The frequency of diabetes mellitus, according to the information obtained, was in the proband material 45 cases among 2010 males (= 2.24 per cent) and 35 among 2031 females (= 1.72 per cent); i.e. 1 98 per cent for the total number of relatives. In the control material, there were 34 cases among *1836 males (= 1.85 per cent)*, 23 among *1805 females (= 1.27* per cent), i.e. 1.56 per cent for both sexes together. The incidence is thus perhaps a little higher among the relatives of the leukemia patients than among those of the control probands; but it is not significant, since the χ^2 test with Yates' correction gives $\chi^2 = 1.65$, $f = 1$, $20\% > P > 10\%$. There is thus in my material no sure evidence of higher incidence of diabetes mellitus among relatives of patients with leukemia. *Bartels* found the frequency of the disease in his normal material to be, for the categories: sibs, parents and brothers and sisters of parents together, 1.7 ± 0.15 per cent. The frequency for the corresponding categories of relatives in my control material is in good accordance with this, namely 1.7 per cent. For the same categories in the patient material the figure is 2.1 per cent.

3 CONCLUSION

Neither the data from the literature nor my own investigations concerning endocrine disorders in patients with leukemia

and their relatives furnish any basis for the hypothesis of a relationship between leukemia and hyperthyreosis, hypothyreosis or diabetes mellitus, since there is no definite evidence that any of these diseases are more frequent in leukemia patients and their families than normally.

Chapter V

GENETIC RELATION BETWEEN LEUKEMIA AND CANCER

It is only in recent times it has become evident that there is a close relationship between leukemia and cancer, a viewpoint based not least on observations made on fowls and inbred strains of mice. The interest has centered not only on the demonstration of pathoanatomic traits common for the two diseases, but also on drawing general biologic and pathophysiologic parallels between them. In the present study I shall attempt to shed some light on the question from the genetic point of view.

1. LEUKEMIA AND CANCER IN THE SAME PATIENT

If there is a genetic relation between two diseases, their coexistence in the same individual should, provided that all other conditions are equal, be so frequent that it cannot be explained as simply incidental. If, on the other hand, an unusually frequent coexistence of them in the same patient can be demonstrated, it will support the concept of a hereditary disposition to them both, unless their simultaneous or successive occurrence can be explained as due to some other cause.

Instances of leukemia and cancer in the same patient have been recorded by several observers. In 1941 *Engelbreth-Holm*

TABLE 10 Authentic Cases of lymphogenous Leukemia and Cancer in the same Patient

Author	Sex	Age when Tumor was diagnosed	Site of Tumor	Microscopy	Age when Leukemia was diagn.	White cells per cmm of Blood	Lymphocytes per Cent	Tumor of lymph Nodes	Splenomegaly	Necropsy	Organs involved by leukemic infiltration
Lamois & Regaud	f.	58	Uterine cervix	+	58	120,000	>90	+	+	+	Liver and kidney
Marischler	m	61	Adrenal	+	61	96,000	83	+	+	+	Lymph nodes
Fuhs	„	56	Skin	+	56	38,000	high	+	+	—	
Scheuller	„	62	„	+		38,000	78			—	Skin
Schreiner & Wehr	„	61	„	+	61	112,000	94	+	+	—	
„ „	„	70	Breast	+	70	24,000	75	+		—	
„ „	„	49	Lung	+	49	149,000	92	+		+	
„ „	„	66	Skin	+	66	189,000	97	+	+	—	
Bruckner	f	63	Uterine cervix	+	61	400,000	97	+	+	—	
Pulvertaft	m	66	Lip	+	70	226,400	>90	+		—	Lymph nodes
Reich	„	55	Sigmoid	+	55	103,000	95			+	Bone marrow
Penzold	„	79	Stomach	+	75	113,000	93	+		+	Liver and lymph nodes
Dustin	„	70	„	+	70	53,600	83	+	+	+	„ „ „
Engelbreth-Holm	„	51	Lower lip	+	66	115,800	90	+	+	—	
„	f	61	Skin	+	71	48,200	98	+	+		
„	„	69	„	+	69	75,400	90	+	+		
„	m	72	„	+	76	46,400	82	+	+	—	
„	„	75	„ + sarcoma	+	76	53,400	95				Bone marrow
„	„	80	Penis	+	82	26,440	64	+			„ „
„	f	83	Skin	+	83	62,200	92	+	+	—	
Holz	„	3	Kidney	+	3	9,200	96	+	+	—	„ „
Kast	m	68	Stomach	+	68	32,800	97	+	—	+	Liver and bone marrow
Gettler	?	74	Skin	+							Confirmed histologically and hematologically
Ovnbol & Terkildsen	m	31	Breast	+	61	144,600	91				
		60	Prostate	+							
Morrison et al	„	58	Pancreas	+	58	66,000	78	+	+	+	Liver and kidney
Videbæk	„	62	Skin	+	62	226,000	89	+	+		

6*

TABLE 11

Authentic Cases of Lymphosarcoma and Carcinoma in the same Patient

Author	Sex	Age when Carcinoma was diagnosed	Site of the Carcinoma	Microscopy	Age when Leukemia was diagnosed	Site of the Lymphosarcoma	Microscopy	Necropsy
Kreibig	?	64	Cecum	+	64	Small intestine	+	+
Schuback	m	52	Stomach	+	52	Stomach	+	+
Warwick	,,	45	•	+	45	Cecum	+	+
Bugher	,,	68	Prostate and pancreas	+	68	•	+	+
Engelbreth-Holm	,,	69	Testis	+	75	Rhinopharynx	+	+
		70	Skin	+				
•	f	24	Ovaries	+	23	Tonsil	+	+

TABLE 12

Authentic Cases of myelogenous Leukemia and Carcinoma in the same Patient

Author	Sex	Age when Tumor was diagnosed	Site of Tumor	Microscopy	Age when Leukemia was diagn	White Cells per cmm of Blood	Myeloblasts and Promyeloc pr Cent	Myelocytes per Cent	Splenomegaly	Tumor of Lymph Nodes	Necropsy	Organs involved by leukemic Infiltration
Whipham ...	m.	23	Pancreas	+	23	more w c than r c.			+	—	+	
Burg ..	f	42	Stomach	+	42	187,000		65	+		+	
Heim	„	45	Uterine cervix	—	44	300,000	many	many	+			
Zadek . .	„	43	Stomach	+	42	200,000	about 6	about 24	+		+	
Cabot	„	60	Breast	+	61	16,000		many	+	—	+	Spleen and Liver
Engelbreth-Holm	„	40	Uterine cervix	+	50	279,000	25	23	+	—		
„	„	54	„ „	+	60	253,000	34	17	+			
Morrison et al . ..	m	62	Rectum	+	64	6,500	100					
Videbæk .	f	45	Lymph Nodes	+	46	13,800	90	1				Retina

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Schuback	m	52	Stomach	+	52	Stomach	+	+
Warwick	„	45	•	+	45	Cecum	+	+
Bugher	„	68	Prostate and pancreas	+	68	•	+	+
Engelbreth-Holm	„	69	Testis	+	75	Rhinopharynx	+	+
		70	Skin	+				
•	f	24	Ovaries	+	23	Tonsil	+	+

cannot conclude anything certain with regard to the frequency with which cancer and leukemia coexist in the same patient. To determine this with any degree of certainty will hardly be possible until a great number of necropsies shall have been made with particular view to the solution of the problem; because many cases of cancer are only discovered by systematic inspection and routinely carried out microscopies of the various organs. Besides, there has until recently, when cancer was present, been a tendency to regard any simultaneous findings of leukemic nature as expressions for a leukemoid state. The following figures must therefore be considered as minima.

Schreiner & *Wehr* (1934) found among 90 patients with leukemia and 165 with lymphosarcoma 4 cases of carcinoma combined with lymphogenous leukemia. *Zadek* (1933) found cancer in 2 of 23 patients with myelogenous leukemia. *Moeschlin* & *Rohr* (1939) found at necropsies on 50 patients with myelogenous leukemia another malignant tumor in 5 of them (10 per cent) *Engelbreth-Holm* (1941) found cancer in 2 of 15 patients with myelogenous and 7 of 31 with lymphogenous leukemia (i.e in about 20 per cent of the 47 with leukemia), and in 2 of 36 with lymphosarcoma That is to say that he found cancer in about 13 per cent of all the 82 patients, and he showed that this frequency was much too great to be due to coincidence. *Kirshbaum* & *Preuss* (1943) found among a necropsy material of 14,400 patients 123 cases of leukemia, and only in 2 of these also cancer In my material of 310 leukemia patients there are only 3 in which also cancer could be demonstrated (one of them has before been published by *Engelbreth-Holm*, cf. also Tables 10 and 11), but some of the 310 are still living We thus see that the statements with regard to coexistence of the two diseases in the same patient vary considerably,—from 2 to 20 per cent,—probably because the examination of the materials did not in all cases include necropsy or were not undertaken expressly with the view of ascertaining the incidence of cancer

It has been pointed out that the lymphogenous type of leukemia was the one with which cancer,—especially skin can-

published a study based on his own observation of 11 such cases together with 11 from the literature. He noted that the complicating cancer was oftenest found in elderly patients with lymphogenous leukemia and in a remarkably large proportion of the cases,—about 50 per cent,—was carcinoma of the skin; from which he concluded that either the incidence of lymphogenous leukemia in individuals of advanced age must be higher than formerly supposed, or there must between lymphogenous leukemia and especially carcinoma of the skin be a relationship of hitherto unknown nature. In Tables 10, 11, and 12, I have recorded, besides *Engelbreth-Holm*'s 22 cases, 2 cases observed by myself and 17 others from the literature, thus obtaining a material of 41 well substantiated cases, in which leukemia and cancer were coexistent in the same patient. Cases of localised leukemia and leukemic blood picture,—for instance lymphosarcoma-cell leukemia, chloroma, myeloma, and endothelioma combined with monocytic leukemia,—are not included. Neither are a few, not fully elucidated cases: *Saar*'s (1929) of stomach cancer and gastric lymphosarcoma, *Zadek*'s (1933) of breast cancer and chronic myelogenous leukemia, *Hoffmann*'s (1934) two cases of cancer and chronic myelogenous, and a third of cancer and chronic lymphogenous leukemia, *Schreiner* & *Wehr*'s (1934) two cases of cancer and lymphogenous leukemia, *Moeschlin* & *Rohr*'s (1939) five cases of cancer and myelosis, and *Kirshbaum* & *Preuss*'s (1943) of myelosarcoma and acute myelogenous leukemia. In a few cases, the original communication has not been available: *Ferrero* & *Gedda* (1933) angiosarcoma and chronic myelogenous leukemia, *Shal* (1933) cancer of the peritoneum and lymphogenous leukemia, and *Denoyer* (1936) larynx cancer and leukemia. Neither has a case of stomach cancer and chronic lymphogenous leukemia reported by *Bichel* in 1940 been included, because it seems doubtful if the patient really had leukemia. At necropsy no signs of the disease could be demonstrated, and also the terminal blood picture (12,800 white cells per cmm., with 2.3 per cent of lymphocytes) speaks against that diagnosis.

From the tabulation of the hitherto published cases we

of the simultaneous occurrence of the two conditions, since the skin cancer oftenest has been present long before the leukemia was diagnosed Moreover, most of the patients in the material here presented are selected cases, in so far as they were not leukemic patients in whom skin cancer had been demonstrated, but a great many of them were cancer patients who later developed symptoms of lymphogenous leukemia. Another element of uncertainty is introduced by the fact that not all the cases came under necropsy examination, which might have disclosed cancer of the viscera Necropsy was only performed on 8 of the 25 patients with lymphogenous leukemia plus cancer, and in all these the complicating cancer was visceral.

On the whole, it seems doubtful if there is any particular relation between lymphogenous leukemia and cancer, especially cancer of the skin. *Engelbreth-Holm* suggests that the frequent coexistence of the two diseases may be due to the incidence of lymphogenous leukemia in elderly persons being considerably higher than hitherto supposed, and this seems to be confirmed by Fig 2, where this disease shows a maximum incidence at sixty-five years of age, while *Ward* (1917) and *Minot & Isaacs* (1924), for instance, found the highest incidence at about fifty years of age. It also seems that, on the whole, the number of cases of leukemia is *increasing* during recent years (*Bethell, 1943*)

Table 10 further shows that the combination of lymphogenous leukemia and cancer is found especially in males (19 of the 25 patients), while Table 12 shows that the combination of myelogenous leukemia with carcinoma oftenest occurs in females (7 of the 9 patients) This may be partly accounted for by the fact that chronic lymphogenous leukemia has a preference for males, while chronic myelogenous leukemia is more common in females; but this cannot be the full explanation On the whole, the material is too small, however, to warrant the formulation of any definite theories on the subject.

Fig 7 shows the distribution by age of the patients in whom lymphogenous leukemia and cancer coexisted, compared with that of 127 patients with chronic lymphogenous leukemia.

cer,—was particularly often associated; and, in fact, as the Tables show, this was the combination in 25 of the 41 cases listed. Chronic lymphogenous leukemia was in 11 cases associated with carcinoma of the skin, in 1 with carcinoma of the penis, in 2 with carcinoma of the lip; lymphosarcoma in *6 cases, and chronic myelogenous leukemia in 9 cases,* associated with carcinoma (in none of them with carcinoma of the skin). It may at first glance seem strange that the association of cancer with lymphogenous leukemia is three times as frequent as the association with myelogenous leukemia (25:9); but in the first place chronic lymphogenous leukemia is undoubtedly more frequent than chronic myelogenous (Table 1), in the second place patients with chronic lymphogenous leukemia are on the average older (Fig. 2). In my material, the average age is for 127 patients with the chronic lymphogenous type 60.8 years, for 79 with the myelogenous type 50.5 years. The ratio between the number of patients with the two types of the disease is thus about 3:2, the average age for the two groups respectively 60 and 50 years. According to a statistical analysis by *Clemmesen* (1946) of yearly cancer mortalities per 10,000 of population in different countries, according to age distribution, about 40 persons die of cancer at the age of sixty years, about 20 at the age of forty. This is to say that the expected mortality from cancer among patients with chronic lymphogenous leukemia is about 3 times as high as the expected mortality from cancer among patients with myelogenous leukemia. Thus, there does not seem to be any difference in the frequency with which the two types of the disease are likely to occur coexistent with cancer.

The relatively frequent occurrence, especially of skin cancer, in connexion with chronic lymphogenous leukemia has, as already said, been pointed out and discussed before (*Engelbreth-Holm*), but has never been satisfactorily accounted for. That cancer sometimes develops in cutaneous areas involved with leukemic infiltrations is undoubted (*Scheuffler*, 1933), but this cannot,—except perhaps in rare cases,—be the explanation

There is a slight shift to the right of the cases complicated by cancer, expressed in the average age for these, which is 66.7 years, as against the normal 60.8 years. The average age for the patients with lymphogenous leukemia plus visceral cancer is 62.3 years, for those in whom the complicating tumor is skin cancer 69.5 years. As already pointed out by *Engelbreth-Holm*, leukemia combined with skin cancer is thus in a marked degree a condition belonging to high old age.

Fig. 7 further shows the distribution by age of the patients listed in Table 12, on the background of the age incidence of 79 cases of chronic myelogenous leukemia. The average age for the cases with concomitant carcinoma (50.2 years) does not deviate from the normal (50.5 years).

Considering that, on the average, patients with multiple cancer die ten to fifteen years before the age at which they would have died if they had only had the cancer which first developed (*Bugher*, 1934) it seems surprising that the leukemic patients with a complicating tumor are not younger. I cannot offer any explanation of this except the smallness of the material and the fact that most of these tumors were skin cancers of which they had been cured.

3. *Conclusion.*

Though no systematic attempt has *yet been made* to ascertain how often leukemia and cancer occur in the same patient, the frequency of *their coexistence* is undoubtedly so high that it cannot be simply *incidental*. Though chronic lymphogenous leukemia *is more* common, and generally develops at a higher age than chronic myelogenous leukemia, *both* forms are equally apt to occur together with carcinoma. Lymphogenous leukemia seems particularly often to be combined with skin cancer, but this observation loses part of its value through the *fact that* lymhogenous leukemia in people of advanced age has been *found* to be more *frequent* than hitherto supposed.



Figure 7 —Charts showing Age Incidence of chronic myelogenous Leukemia (79 Cases) and chronic lymphogenous Leukemia (127 Cases) ☐, and of the Cases (respectively 9 and 25) in which the Leukemias were combined with Carcinoma ■

There is a slight shift to the right of the cases complicated by cancer, expressed in the average age for these, which is 66 7 years, as against the normal 60 8 years. The average age for the patients with lymphogenous leukemia plus visceral cancer is 62.3 years, for those in whom the complicating tumor is skin cancer 69.5 years. As already pointed out by *Engelbreth-Holm*, leukemia combined with skin cancer is thus in a marked degree a condition belonging to high old age.

Fig. 7 further shows the distribution by age of the patients listed in Table 12, on the background of the age incidence of 79 cases of chronic myelogenous leukemia. The average age for the cases with concomitant carcinoma (50.2 years) does not deviate from the normal (50 5 years).

Considering that, on the average, patients with multiple cancer die ten to fifteen years before the age at which they would have died if they had only had the cancer which first developed (*Bugher*, 1934) it seems surprising that the leukemic patients with a complicating tumor are not younger. I cannot offer any explanation of this except the smallness of the material and the fact that most of these tumors were skin cancers of which they had been cured

3 *Conclusion*

Though no systematic attempt has yet been made to ascertain how often leukemia and cancer occur in the same patient, *the frequency* of their coexistence is undoubtedly so high that it cannot be simply incidental Though chronic lymphogenous leukemia is more common, and generally develops at a higher age than chronic myelogenous leukemia, both forms are equally apt to occur together with carcinoma Lymphogenous leukemia seems particularly often to be combined with skin cancer, but this observation loses part of its value through the fact that lymhogenous leukemia in people of advanced age has been found to be more frequent than hitherto supposed

2 LEUKEMIA AND CANCER IN THE SAME FAMILY

Reports of the finding of malignant tumors in relatives of leukemia patients are few. *Decastello* (1925) noted that four sibs and the mother of a patient with chronic myelogenous leukemia were stated to have died of carcinoma. *Maack* (1940) mentions that the demonstration of squamocellular carcinoma in one of three brothers was particularly interesting by the fact that the two others had leukemia. *Rohr* (1945) recorded without further comment the existence of malignant tumors in 12 pedigrees of 22 patients with leukemia, and thought that this confirmed the view of leukemia as a tumor disease. Conversely, *Jacobsen* (1946) found in the families of 200 cancer patients 3 persons with leukemia, but in the families of 200 sound individuals only 1 case of that disease; and also this points to a relationship between cancer and leukemia.

In a group by themselves stand, however, *Braun*'s (1912) observations of mediastinal sarcoma, malignant mesenterial lymphoma, and malignant lymphoma with subsequent leukemia, respectively in a sister and her two brothers, *Richards*' (1921) of lymphosarcoma in a sixteen-year-old girl and lymphogenous leukemia in her father, and *Hogrefe*'s (1945) of plasmocytic reticulosarcoma in a family in which there were 2 cases of leukemia; because these tumors, which all had arisen from the hemopoietic system, are more nearly related to leukemia than carcinomas, and are, in fact, probably a form of localised leukemia, so that the cases may with good reason be regarded as observations of familial leukemia

The determination of whether the incidence of cancer is particularly high among relatives of patients with leukemia will require a systematic investigation on broad lines, and such an investigation is all the more needed because the neoplastic theory of leukemia is still being discussed, and it might in a new manner shed light on the question whether the process is a malignant tumor.

Author's Investigations.

In the manner described in Chapter I, I have examined the incidence of cancer among the relatives of 209 patients with leukemia and of 200 control probands. Among 4041 relatives of the former there were 319 cases of cancer (= 7.89 per cent), among 3641 relatives of the latter 218 (= 5.99 per cent). The age distribution was the same in the two groups. The incidence of cancer is thus about 32 per cent higher in the patient material than in the control material, a difference which is statistically significant (see Table 14).

That the cancer taint is more pronounced in the families of the leukemic patients than in those of the controls, is also seen from Table 13

TABLE 13
Showing the Incidence Distribution of Cancer in the Families of the Leukemia Patients and the Control Probands

	Number of Families in Patient Material	Number of Families in Control Material
Cancer-free Families	55	76
Families with 1 Case of Cancer	74	65
„ „ 2 Cases	36	35
„ „ 3 „	18	13
„ „ 4 or more Cases	26	11

It will be noticed that there especially in the patient material are many families in which the cancer taint is very pronounced (4 cases or more)

Table 14 shows the incidence of cancer in the different categories of relatives in the two materials If we leave out the categories sons and daughters, in which there are only 3 cases in all, we see that the incidence is highest in the patient material all through, except in the category maternal grandmothers. The cancer incidence here, which is not only higher than for any other group of relatives in the control material,

TABLE 14

Showing the Incidence of Cancer in the different Categories of Relatives of the Leukemia Patients and the Control Probands.

(P is calculateed by a method indicated by *A. Hald*, which enables us to obtain a good approximation to the exact P-value).

Category of Relatives	Patient Material			Control Material			P
	Number of Relatives	Number of Cases of Cancer	Incidence per Cent	Number of Relatives	Number of Cases of Cancer	Incidence per Cent	
Fathers	208	31	14.9	200	18	9.0	$10\% > P > 5\%$
Paternal Grandfathers	182	22	12.1	178	13	7.3	$20\% > P > 10\%$
Maternal Grandfathers .	179	21	11.7	175	17	9.7	$70\% > P > 60\%$
Paternal Uncles	412	26	6.3	363	18	5.0	$60\% > P > 30\%$
Maternal "	402	31	7.7	386	20	5.2	$20\% > P > 10\%$
Brothers	457	18	3.9	393	9	2.3	$30\% > P > 20\%$
Sons	170	—	—	141	1	0.7	$P > 90\%$
Males, total:	2010	149	7.4	1836	96	5.2	$1\% > P > 1‰$
Mothers.	209	28	13.4	200	21	10.5	$50\% > P > 40\%$
Paternal Grandmothers	190	22	11.6	170	16	9.4	$70\% > P > 60\%$
Maternal Grandmothers	190	23	12.1	191	27	14.1	$70\% > P > 60\%$
Paternal Aunts	423	31	7.3	347	20	5.8	$50\% > P > 40\%$
Maternal "	417	33	7.9	350	22	6.3	$50\% > P > 40\%$
Sisters . . .	447	32	7.2	409	15	3.7	$5\% > P > 2\%$
Daugthers .	155	1	0.6	138	1	0.7	$60\% > P > 50\%$
Females, total	2031	170	8.4	1805	122	6.8	$10\% > P > 5\%$
Relatives, total	4041	319	7.89	3641	218	5.99	$1\% > P > 1‰$

but in the patient material is only overtopped by the cancer incidence among the fathers of the probands, is so exceptionally high, however, that it can hardly be the normal for females of that age class That only one category of relatives in the patient material (sisters) shows a cancer incidence significantly higher than the corresponding category in the control material, is because it is not a question of greater preponderance of cancer in the leukemia families. But the fact that the cancer in-

cidence is so uniformly higher in the patient material indicates that the excess is real; which is also seen from the fact that the calculation of P for all the categories of relatives together gives a value much beyond the 5 per cent limit.

The question is now whether this excess incidence is due only to cancer of some definite site being particularly frequent, or to all forms of cancer occurring with greater fre-

TABLE 15.

Showing the Localisation of the Cancer in 319 Relatives of the Leukemia Patients and 218 Relatives of the Control Probands

Site of Tumor	Patient Material				Control Material			
	Males	Females	Total	per Cent	Males	Females	Total	per Cent
Carcinomas:								
Skin	1	3	4	1.3	3	3	6	2.8
Lip	6		6	1.9				
Penis	2		2	0.6				
Vagina, Vulva						3	3	1.4
Upper alim. Tract	2		2	0.6	4	2	6	2.8
Esophagus	21	3	24	7.5	7	1	8	3.7
Stomach	42	38	80	25.0	41	26	67	30.7
Intestine	10	14	24	7.5	9	4	13	6.0
Rectum	11	4	15	4.7	8	3	11	5.0
Pancreas	4		4	1.3	1		1	0.5
Liver	10	4	14	4.4	5	6	11	5.0
Gall-bladder		1	1	0.3				
Abdomen	19	23	42	13.2	8	11	19	8.7
Kidney	1	1	2	0.6				
Urinary Bladder		2	2	0.6	1	1	2	0.9
Prostate	6		6	1.9	2		2	0.9
Testis					1		1	0.5
Upper Air Passages	1		1	0.3				
Lung	4		4	1.3		1	1	0.5
Breast		33	33	10.3		26	26	11.9
Uterus		28	28	8.8		18	18	8.3
Ovaries		3	3	0.9		5	5	2.3
Sarcomas		5	5	1.6		1	1	0.5
Other Forms	9	8	17	5.3	6	11	17	7.8
All Sites	149	170	319	99.9	96	122	218	100.2

quency, in the patient material. In Table 15 are shown the absolute and relative frequencies of cancer of various sites. There is no marked difference between the two materials as regards the distribution per cent, all the various sites being, on the whole, equally represented. That the rates for cancers of the esophagus and the abdomen are somewhat higher in the leukemia families than in those of the control, and, on the other hand, the rates for stomach cancer higher in the latter, is no doubt due, besides to the biologic variation, to difficulties of diagnostication, because the rates for the three sites together are nearly the same in the two materials, namely 45.8 and 43.1 per cent, respectively.

If the frequent coexistence of leukemia and skin cancer in the same patient were due to the operation of hereditary factors common for the two diseases, it would be reasonable to expect a particularly great excess incidence of skin cancer among the relatives of the leukemia patients, but in the present material, at least, there is none such. The forms of cancer whose development by reason of their site undoubtedly are particularly apt to be conditioned by exogenous factors, namely cancer of the skin, the prolabium, the penis, the vagina and vulva, are about equally frequent in the two materials, constituting together respectively 3.8 and 4.1 per cent of all the cases in these. That on the contrary, the figures are so small, can only be because these forms of cancer seldom are the cause of death or require a treatment which attracts particular attention, and therefore have not been brought to light in the course of my investigations. The result of these observations is that there among the relatives of the leukemia patients can be demonstrated a relatively high incidence of cancer as a whole, due to an excess incidence of all forms of the disease.

The next question is if any of the various forms of leukemia is particularly "malignant" in such a manner that relatives of patients with that type of the disease are more likely to carry the cancer taint than the relatives of patients with other forms of leukemia. Table 16 shows the incidence of cancer as a whole among relatives of patients with various forms of leukemia.

It will be seen that the relatives of those with chronic lymphogenous leukemia have only a slightly higher cancer rate than the relatives of those with chronic myelogenous. The difference can be explained by the fact that the probands for the former group are, on the average, about ten years older than the probands for the latter (see Table 7); consequently, also many of their relatives are older (specially noticeable as regards the category: sibs) and the cancer incidence among them therefore higher. In the same way it is understandable that

TABLE 16

Showing the Incidence of Cancer among Relatives of Patients with various Forms of Leukemia and among Relatives of the Control Probands

Type of Leukemia	Males			Females			Males + Females		
	Number of Relatives	Number of Cancer Cases	Incidence per Cent	Number of Relatives	Number of Cancer Cases	Incidence per Cent	Number of Relatives	Number of Cancer Cases	Incidence per Cent
Chronic lymphogenous	699	58	8.3	730	73	10.0	1429	131	9.2
Chronic myelogenous	546	43	7.9	540	51	9.4	1086	94	8.7
Acute	756	48	6.3	747	46	6.2	1503	94	6.3
Control Material	1836	96	5.2	1805	122	6.8	3641	218	6.0

the cancer incidence among the relatives of patients with acute leukemia is smaller than among the relatives of those with chronic lymphogenous leukemia. That the difference here is greater than between the *two other leukemia* groups is probably only because the probands with acute leukemia were, on the average, twenty to thirty years younger than those with chronic leukemia (see Table 7).

The question whether one form of leukemia is more "malignant" than another may also be formulated in this way:

Is the cancer risk greater for the relatives of patients with one particular type of leukemia than for those of patients with another type of the same disease?—understanding by cancer risk the probability of the relative in question getting cancer if he lives through all the age classes in which it is possible to get cancer; which practically means them all. According to *Weinberg* (1935) and *Strömgren* (1938), the disease risk for any category of relatives can be calculated if we know

(1) the distribution by age of patients with the disease in question,—in this case cancer in general;

(2) the age distribution of the population corresponding to (1);

(3) the age distribution of the members of the category of relatives in question.

Ad (1): Thanks to the Danish Cancer Registry we posses an reliable analysis of the distribution, by age and sex, of cancer as a whole, i.e. cancer of all sites, in Denmark. The figures for 1942, comprising 3982 males and 5066 females, have been published by *Jacobsen* (1946), and are also in this study used as basis for the estimation of the cancer risk.

Ad (2): The population corresponding to these 9048 cancer patients is the country's population in 1942. It is not stated precisely for 1942, but per Nov. 5th, 1940 (Statistisk Aarbog, 1942).

Ad (3): The age distribution within each category of relatives has been figured out on the basis of the pedigree charts (Tables 3 and 4).

Calculated in this manner, the cancer risk for relatives of patients with the different forms of leukemia is:

for all relatives of patients with chronic lymphogenous leukemia: 30 per cent,

for all relatives of patients with chronic myelogenous leukemia: 31 per cent;

for all relatives of patients with acute leukemia: 33 per cent;

for all relatives of 200 control probands: 22 per cent.

This agreement between the percentages for the different

varieties of leukemia shows that the cancer risk for the relatives is not dependent on the type of the disease, and acute leukemia, which clinically is a particularly malignant type, is thus not conditioned by a heavier cancer taint than either chronic lymphogenous or chronic myelogenous leukemia.

The Cancer Risk for the different Categories of Relatives.

The relation between leukemia and cancer which is evidenced both by the frequent coexistence of the two diseases in the same patient and by the relatively high incidence of cancer in the families of patients with leukemia, is rather of constitutional nature and dependent on chromosomal factors. Even if we consider the demonstrated relation as a hereditary disposition to both diseases, it must presumably also be dependent on one or several genes the hereditation of which is subject to certain laws. To demonstrate the existence of these it is not sufficient to know the number of manifestly affected individuals in the different categories of relatives; also the number of latent carriers must be known, which is expressed by the cancer risk

The high average incidence of cancer in the patient material makes it evident that also the cancer risk for the different categories is relatively high. But a slight variation in the number of cases of cancer in one category will alter the figure for the risk of the disease in this category considerably; and as the number of observed cases in each category is rather small, the total cancer risk will unavoidably be more or less uncertain. It is therefore not surprising that they vary in a seemingly rather irregular manner. As Table 17 shows, the risk of getting cancer is highest for fathers and sisters, but not very great for mothers and brothers Moreover, the risk seems to be greater for the parents than for the brothers and sisters of these, and the figures are higher for all the male categories of relatives than for the corresponding female except the sister group But from Table 14 it is seen that also in the control material the percentage of cancer cases is higher among the

7*

TABLE 17.

Showing the Cancer Risk for the different Categories of Relatives

Category of Relatives	Number of Cancer Cases	Percentage of Cancer Cases	Cancer Risk per Cent	
Fathers	31	15	48	
Paternal grandfathers	22	12	36	
Maternal "	21	12	36	
Paternal uncles	26	6	25	
Maternal "	31	8	34	
Brothers	18	4	34	
All Males	149	7.4	35	31
Mothers	28	13	36	
Paternal grandmothers	22	12	24	
Maternal "	23	12	27	
Paternal aunts	31	7	23	
Maternal "	33	8	25	
Sisters	32	7	47	
All Females	170	8.4	29	
Males in Control Material	96	5.2	21	22
Females in Control Material	122	6.8	23	

parents than among their brothers and sisters, and this can only mean that the investigation, such as it has been conducted, has failed to disclose all the cases of cancer in these more distant categories of relatives. Since the same method and the same care was employed in the collection of the two materials, it is probable that also in the patient material too few of the cancer cases among the brothers and sisters of the parents have been brought to light, and that the cancer risk figures for these groups therefore are too small To reduce these elements of uncertainty it would be best if several of the categories of relatives could be thrown together (Table 17)

So far as the question: dominance or recessivity is concerned, the three groups (1) parents, (2) sibs and (3) grand-

parents + brothers and sisters of the parents are of interest. The cancer risk figures for them are respectively 41, 40 and 26 per cent, which rather points to dominance (cf. the table p 160 in Hultkrantz & Dahlberg's treatise). A conclusion respecting the mode of inheritance on the basis of such cancer risk figures presupposes, however, that cancer is a genetic entity, and if this is the case is not yet known. It is thus possible that genetically it is absurd to operate with the concept cancer as a whole

We see that the cancer risk figures for the relatives of patients with leukemia vary from 23 to 47 per cent, with an average of at least 31 per cent, and are independent of the type of the leukemia. The figures for the individual categories or relatives are, of course, minima, and are very uncertain. To obtain reliable figures would hardly require a larger proband material than the present, but a possibility of ascertaining with greater certainty if all the relatives in the categories investigated had, or had had, cancer Such a possibility will not exist, however, until a thoroughly reliable registration of all cases of cancer shall have been carried out for a considerable number of years

3 CONCLUSION

The results of the preceding examinations justify the conclusion that there exists a relation between leukemia and cancer, demonstrable by the fact that the latter disease is more frequent in the relatives of patients with leukemia than normally, and made probable by the noticeably frequent coexistence of the two diseases in the same patient, which rather strongly suggests the existence of a constitutional association between them The result of the investigation thus agrees with, and supports, the now prevailing concept of leukemia as a malignant neoplasm, a cancer of the blood-forming tissue not essentially different from other cancers except by the fact that the hemopoietic apparatus and the blood as a liquid tissue hold a place of their own in the organism

Just as *Jacobsen* (1946) has demonstrated among relatives of patients with breast cancer an indubitable increase not only of cancer of that site, but of cancer in general, thus can there in the relatives of patients with leukemia be demonstrated not only a high incidence of leukemia, but also a high incidence of cancer as a whole. There evidently exists a general, hereditary predisposition to cancer, including a predisposition to leukemia. Under the well-founded preassumption that leukemia is a neoplasm, the *result of my investigation thus confirms* the theory already emitted in 1925 by *Bauer* and since supported by a long line of workers, among others *Waaler* (1932), *Schinz* & *Buschke* (1935) and *Jacobsen* (1946), according to which the development of cancer is conditioned by two factors: partly by a non-specific hereditary predisposition to the disease, partly by a factor determining for the localisation of the tumor to some definite organ or organic system. The non-specific disposition, *Jacobsen* believes to be inherited dominantly and to be found in about 10 per cent of the population. Of the localisation of the cancer to the breast he thinks that it is determined by endogenous extrachromosomal or exogenous factors, though, as a matter of fact, his figures rather point to also the localising factor being chromosomal. My own investigations do not warrant any conclusion with regard to the mode of inheritance of this general predisposition to cancer, but the figures for the risk of the various categories of relatives getting the disease are,—under the preassumption that cancer as a whole constitutes a genetic entity,—rather suggestive of dominance. The special localisation of the cancer to the leukon *is chromosomal*, but *my reason for believing that this "gene of* localisation" is not a necessary condition for the development of leukemia is that this disease in most cases occurs without there being any demonstrable hereditary leukemia taint. In *three-fourths of the cases there was a more or less pronounced* hereditary tendency to other forms of cancer, in one-fourth there was no demonstrable cancer taint, at all, though of course there may in the family have been latent carriers or perhaps the localisation of the cancer to the leukon may have been due

to exogenous factors. It is thus probable that several factors co-operate in the production of leukemia, one of them being hereditary predisposition, as we also know from experiments on animals.

In the strictest sense we cannot, however, speak of "inheritance of leukemia", since it is not, of course, leukemia as such that is inherited; but the disease must be considered as a condition which may develop as the result of the combined action of extrachromosomal factors on one or several genes whose rôle in the production of leukemia in man from all that we now know is beyond doubt. It is not known with certainty on what particular condition of the cell the development of *cancer* depends, or what gene, or genes, are responsible for that condition. It may be a general weakness of the cells, *perhaps a diminution* of their power of differentiation, possibly combined with an increased capacity for regeneration; *perhaps* it is a *question* of a hereditarily determined tendency to mutation. Our knowledge about the determining external factors is slight, but they are, of course, closely bound up with the fact that leukemia does not manifest itself until after some time, when the individual has reached a certain age. They explain perhaps *the* curious age distribution of the disease, with peaks *of* incidence in early childhood and, later, between the fiftieth and seventieth years of age, while relatively few cases occur during the decades between

The probability of the leukemia developing at an earlier period of life is greater when the genetic conditions are particularly favorable, as when there is a demonstrable hereditary taint. On the other hand, the possibility of the occurrence of the disease no doubt becomes greater with advancing age even though the mosaic of the genes is less favorable for its development, but perhaps it will not manifest itself because the sum of external influences does not get time to become sufficiently great during the individual's remaining span of life. That the leukemia occurs now in one form, now in another, may of course be due to differences in the degree of the genetic constitution, and if that is the case it must be supposed that

e leukemias seem to be an entity genetically, it is most
able that the type the disease assumes in the individual
is determined by the general conditions of his life, taken
e widest sense.

he practical result of the investigation is that while there
ly little likelihood that other members of a family should
articularly liable to get leukemia because one relative is
ted with that disease, there is up to 50 per cent's risk of
ear relatives of a leukemia patient getting cancer (unless
die from some other cause). Though this will hardly lead
igenic measures being taken, it is important that the
its, and brothers and sisters of the parents, of a child af-
d with leukemia, as well as the brothers and sisters of
atient, should know that they are particularly susceptible
t cancer, so that they, by being aware of this fact, may
o it that any appearing symptom of developing tumor is
overlooked or neglected. That treatment in case of any
symptom appearing is instituted as early as possible re-
s, however, first of all, that the patient's physician is
e of this great risk and bears it in mind when he observes
of the vague and unspecific symptoms with which cancer
first announces itself.

PEDEGREE CHARTS
AND
CASE HISTORIES

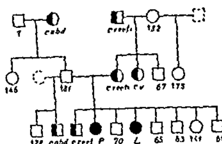
This section contains the case histories of the 203 probands together with the pedigree charts of the 206 families to which they belong, comprising the categories of relatives which have been the object of investigation. The case history of each proband contains besides a brief anamnesis the data on which the diagnosis rests, and similarly are briefly given, with regard to the affected relatives, the data substantiating the diagnosis of their respective diseases, which in the charts are indicated by special symbols as shown below.

The case histories are arranged in the following order, according to the proband's type of leukemia and his (her) age at the time when the disease was recognised:

Nos. 1— 14: Families with several cases of leukemia.
15— 78: Probands with chronic lymphogenous leukemia.
79—130 „ „ „ myelogenous „
131—153: „ „ acute lymphogenous „
154—167. „ „ „ myelogenous „
168—205· „ „ stem-cell „
206· „ „ monocytic „

KEY TO SYMBOLS

leukemia	Graves' disease.
cancer	myxedema.
blood disease other than leukemia	diabetes mellitus.
sex unknown	stillborn
enzygotic twins	fraternal twins.



Pedigree 1

PROBAND (State Hospital, service B, no 945/36)—Book-keeper. Formerly well, never pregnant. When 63 hemorrhagic diathesis, increasing fatigue, hazelnut-sized lymph node in left axilla, spleen extending to mid-line and iliac crest Hemoglobin 77 %, white cells 140,600, myeloblasts 10½ %, promyelocytes 2½ %, neutrophile metamyelocytes 2 %, staff cells 16 %, segmented neutrophils 26 %, eosinophils 10 %, basophils 11 %, lymphocytes 11 % Basal metabolism 147 % Wassermann negative Roentgen therapy temporarily good effect. Followed for 2 years. Necropsy (350/36): Spleen 940 g Liver 1,800 g—Diagnosis *chronic myelogenous leukemia*

SISTER (Bispebjerg Hospital, service B, no 3/15)—Housewife Formerly well, never pregnant. When 42 found to be suffering from enlarged spleen A year later admitted with general symptoms of anemia, stomatitis, spleen extending to right of the umbilicus and to iliac crest, liver palpable 5 cm below the costal margin Hemoglobin 55 %, white cells 60,000, myelocytes 12 %, segmented neutrophils 85 %, lymphocytes 3 %. Followed for about 1 year Necropsy (136/15) spleen 1,940 g, bone marrow greyish red—Diagnosis *Chronic myelogenous leukemia.*

BROTHER—Died June 10th, 1945, aged 71, of cancer of the rectum (death certificate)

HALF-BROTHER—Died Feb 1st, 1923, aged 58, of cancer of the abdomen (death certificate)

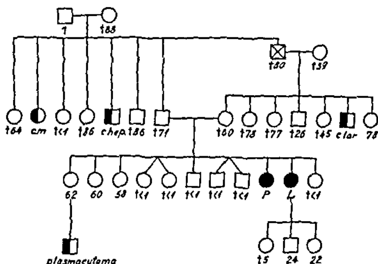
MOTHER—Died July 14th, 1902, aged 59, of cancer of the rectum (death certificate)

MOTHER'S SISTER—Died June 30th, 1924, aged 57, of stomach cancer (death certificate)

MOTHER'S FATHER—Died May 13th, 1905, aged 65, of cancer of the rectum (death certificate)

FATHER'S MOTHER—Died July 8th, 1861, aged 56, according to the death certificate of "internal disorder" Had for about 6 months before been very feeble and emaciated, with somewhat yellowish complexion

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Pedigree 2

PROBAND (Municipal Hospital, service 2, no 129/38).—Housewife Formerly well, never pregnant. When 40 loss of weight and fatigue; spleen about 10 cm. below costal margin; no enlargement of liver or lymph nodes Hemoglobin 70 %, white cells 6,400 per cmm, myeloblasts 15 %, myelocytes *14 %, segmented neutrophils 63 %, basophils 3 %, lymphocytes 5 %. Good effect of roentgen therapy Followed for 1 year. Toward the end white* cells 50,000, myeloblasts 66 %. Necropsy (648/38) Liver 26 × 25 × 10 cm, spleen 32 × 17 × 10 cm—Diagnosis: *Chronic myelogenous leukemia.*

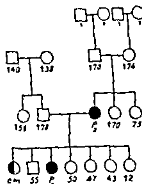
SISTER—(According to *Hogrelle's* report:) Housewife Three childbirths. As child scarlet fever complicated by nephritis When 28 pleurisy When 43 admitted to hospital on account of increasing fatigue, swollen lymph *nodes in neck and groin, spleen 5 cm. below umbilicus Hemoglobin 82 %* White cells 12,000, myeloblasts 2 6 %, promyelocytes 11 6 %, metamyelocytes 9 3 %, segmented neutrophils 64 6 %, eosinophils 2.3 %, basophils 0 6 %, lymphocytes 5 6 %, monocytes 2 3 % Roentgen therapy with temporary good effect Eight hospitalisations Followed for 5 years. Died in her home—Diagnosis: *Chronic myelogenous leukemia*

FATHER'S BROTHER—Died Aug 10th, 1927, aged 73, of cancer of the liver (death certificate)

FATHER'S SISTER—Died Feb 28th, 1923, aged 77, of breast cancer (death certificate).

MOTHER'S BROTHER—Died May 29th, 1941, aged 77, of cancer of the larynx (death certificate)

SISTER'S SON—Died June 3rd, 1944, of plasmocytic reticulosarcoma (State Hospital, Copenhagen, neurologic service; no 5289/44)



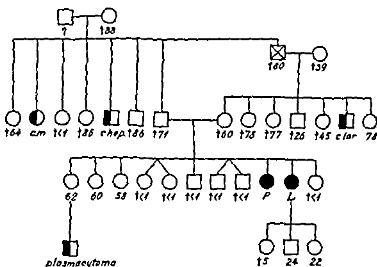
Pedigree 3

PROBAND$_1$ (State Hospital, service A, no 790/44)—Housewife One abortion, no children When 15 diphtheria. Since she was 25 suffering from migraine When 49 considerable loss of weight, hemoglobin 52 %, white cells 400,000 Was given roentgen treatment with good effect temporarily. Two years later marked enlargement of spleen and liver; hemoglobin 55 %, white cells 95,000, promyelocytes 1½ %, neutrophile myelocytes 26½ %, neutrophile metamyelocytes 4 %, staff-cells 14½ %, segmented neutrophils 35 %, eosinophils 4 %, basophils ½ %, lymphocytes 14 %. Wassermann negative Sternal punctate myeloblasts and promyelocytes 33 %. Followed for about 2 years Necropsy (314/44): spleen 2,500 g, leukemic infiltration in liver, spleen, bone marrow and lymph nodes—Diagnosis: *Chronic myelogenous leukemia*

PROBAND$_2$ (Sundby Hospital; service M, no. 1355/38)—Widow Six childbirths When 60 cholelithiasis (cholecystectomy) When 69 admitted for pneumonia, and at the same time universal, moderate enlargement of the lymph nodes was found, and the spleen reaching to 10 cm below the costal margin Hemoglobin 77 %, white cells 128,000, with lymphocytes 98 % Wassermann negative. Roentgen treatment given with temporarily good effect Three years later white cells 139,000, with lymphocytes 94 % Necropsy (196/38) Leukemic infiltration in liver, kidney, spleen, bone marrow and lymph nodes—Diagnosis *Chronic lymphogenous leukemia*

SISTER—Living, aged 57, operated on for breast cancer (Radium Center, Copenhagen, no 36803)

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Pedigree 2.

PROBAND (Municipal Hospital, service 2, no 129/38) —Housewife Formerly well, never pregnant. When 40 loss of weight and fatigue; spleen about 10 cm below costal margin; no enlargement of liver or lymph nodes Hemoglobin 70 %, white cells 6,400 per cmm, myeloblasts 15 %, myelocytes 14 %, segmented neutrophils 63 %, basophils 3 %, lymphocytes 5 % Good effect of roentgen therapy. Followed for 1 year Toward the end. white cells 50,000, myeloblasts 66 % Necropsy (648/38) Liver 26 × 25 × 10 cm, spleen 32 × 17 × 10 cm —Diagnosis. *Chronic myelogenous leukemia*

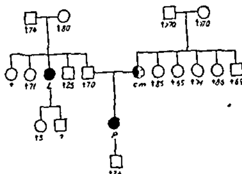
SISTER —(According to *Hogrelle*'s report) Housewife Three childbirths As child scarlet fever complicated by nephritis When 28 pleurisy When 43 admitted to hospital on account of increasing fatigue, swollen lymph nodes in neck and groin, spleen 5 cm below umbilicus Hemoglobin 82 % White cells 12,000, myeloblasts 2 6 %, promyelocytes 11 6 %, metamyelocytes 9 3 %, segmented neutrophils 64 6 %, eosinophils 2 3 %, basophils 0 6 %, lymphocytes 5 6 %, monocytes 2 3 % Roentgen therapy with temporary good effect Eight hospitalisations Followed for 5 years Died in her home —Diagnosis: *Chronic myelogenous leukemia*

FATHER'S BROTHER.—Died Aug 10th, 1927, aged 73, of cancer of the liver (death certificate)

FATHER'S SISTER —Died Feb 28th, 1923, aged 77, of breast cancer (death certificate)

MOTHER'S BROTHER —Died May 29th, 1941, aged 77, of cancer of the larynx (death certificate)

SISTER'S SON —Died June 3rd, 1944, of plasmocytic reticulosarcoma (State Hospital, Copenhagen, neurologic service, no 5289/44)

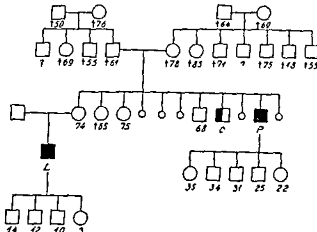


Pedigree 5

PROBAND (County Hospital, Gentofte, service F, no 1410/44)—Housewife Formerly well, never pregnant, had menstruated normally. When 57 hospitalised owing to increasing fatigue Sugillations, spleen palpable 8 cm. below the costal margin, no enlargement of lymph nodes Hemoglobin 72 %, red cells 3,350,000, white cells 181,000, mononuclears 90 %. Terminally, white cells 611,000, nearly all stem-cells Wassermann negative Followed for about 6 months No necropsy—Diagnosis *Stem-cell leukemia.*

FATHER'S SISTER (Municipal Hospital, Copenhagen; service 2, no 98/18)—Housewife Four childbirths When 30 pneumonia, when 41 treated for syphilis For several years suffering from fatigue When 54 stitch in left side below the costal margin, increase of abdominal circumference, the spleen felt enormously enlarged, the lymph nodes in axilla and groin swollen Hemoglobin 55 %, white cells 470,000, with 99 % of lymphocytes, nearly all typical Roentgen treatment without marked effect. Necropsy (137/18)· Spleen enormous, bone marrow greyish.—Diagnosis *Chronic lymphogenous leukemia*

MOTHER—Died March 12th, 1922, aged 71, of cancer of the breast (death certificate)

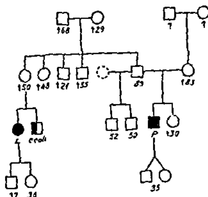


Pedigree 4

PROBAND (Bispebjerg Hospital, service B, no 31/6/42).—Head clerk. When 43 confined to bed for 3½ months owing to severe anemia. When 49 nephrolithiasis When 59 lumbar pains, fever, cough, considerable universal enlargement of lymph nodes, the liver palpable 3 cm below the costal margin No enlargement of the spleen Hemoglobin 72 %, white cells 287,000, lymphocytes 96 % Wassermann negative Leukocyte count rising to 496,000 Roentgen therapy no effect Died at home —Diagnosis *Acute lymphogenous leukemia.*

SISTER'S SON (County Hospital, Holbæk, med service, no. 515/44) — Drainage contractor. Formerly well When 38 for 9 months increasing fatigue, anorexia, loss of weight, palpitations, tinnitus, and finally hemorrhagic diathesis Spleen and liver palpable 3 cm below the costal margin, lymph nodes slightly enlarged Hemoglobin 36 %, white cells 1,760, stem cells 84 %, segmented neutrophils 16 %, thrombocytes 31,000 Sternal punctate. stem-cells 98 % Wassermann negative Died 1 month after admission No necropsy —Diagnosis *Stem-cell leukemia*

BROTHER —Died March 15th, 1942, aged 63, of occult cancer with metastases to the spinal column (death certificate)



Pedigree 7

PROBAND (Municipal Hospital; service 2, no 847/42)—Waggoner For many years suffering from lumbago When 63 admitted with intense pains in the back and marked hemorrhagic diathesis No enlargement of spleen or lymph nodes Hemoglobin 77 %, red cells 3,700,000, white cells 112,000, nearly all myeloblasts and myelocytes Wasserman negative Died 1 week after admission Necropsy (429/42) Leukemic infiltration in spleen and bone marrow—Diagnosis *Acute myelogenous leukemia*

COUSIN (Bispebjerg Hospital, service C, no 17/12/45)—Housewife Two childbirths Formerly nearly always well until she, when 60 years old, was admitted after having suffering for six months from fatigue, itching of the skin and increasing enlargement of the lymph nodes in the neck At admission the nodes in the neck, the axillae and the groin were up to the walnut -sized, the liver and spleen palpable respectively 1 and 8 cm. below the costal margin Hemoglobin 73 %, red cells 2,890,000, white cells 372,000, lymphocytes 99 %, thrombocytes 143,000 Roentgen therapy applied with good effect Followed for 9 months Still living—Diagnosis *Chronic lymphogenous leukemia*

COUSIN—Died March 24th, 1937, aged 46, of cancer of the colon (death certificate)

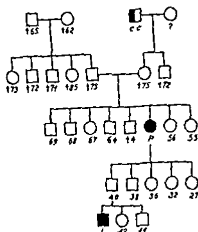
Pedigree 6

PROBAND (Bispebjerg Hospital; service B, died May 21st, 1942).—Housewife Formerly well; 2 childbirths When 29 admitted owing to extreme fatigue. Hemoglobin 47 %, white cells 63,200, segmented neutrophils 8 %, stem-cells 92 %. Died about 1 month after admission Necropsy (no 92/42): liver 7 × 25 × 32 cm, spleen 7 × 10 × 18 cm, of firm consistence, walnut-sized lymph nodes in the mesentery Microscopy report lost—Diagnosis *Stem-cell leukemia*

MOTHER'S SISTER (County Hospital, Hjørring, med service, no 566/42). —Cottager's wife Seven childbirths When 36, and again when 48, maxillary sinuitis; when 42 operated on for salpingitis, when 47 nephropexy When 52 a single attack of cholelithiasis When 53 fatigue, anorexia, loss of weight, cardialgia, tinnitus and depression Admitted owing to hemorrhagic diathesis Spleen and liver moderately enlarged Hemoglobin falling from 60 to 39 %, white cell count increasing to 54,000, myeloblasts 5 %, myelocytes 87 %, segmented neutrophils 7 %, lymphocytes 1 % Sternal marrow very hyperplastic. Wassermann negative Died about 4 months after the appearance of the first symptom Necropsy strong leukemic infiltration in the kidneys—Diagnosis: *Chronic myelogenous leukemia*

FATHER'S BROTHER—Died July 8th, 1945, aged 66, of cancer of the esophagus (Radium Center, Copenhagen, no 30860)

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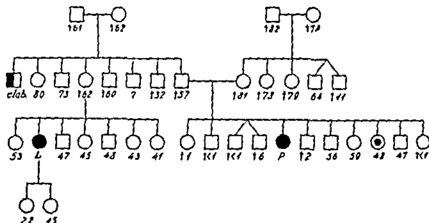


Pedigree 9

PROBAND (County Hospital, Gentofte; service C, no 1274/43)—Housewife Five childbirths When 47 exudative pleurisy, when 51 excochleation of the uterus and roentgen castration on account of pronounced metrorrhagia When 57 tonsillitis and erysipelas of the face Examination showed moderate universal enlargement of the lymph nodes, doubtful splenomegaly, but 14,400 white cells, with 71 % of lymphocytes She has been well since, but blood examination when she was 60 showed hemoglobin 81 %, white cells 86,400, small lymphocytes 91 %, large lymphocytes 4 % Sternal punctate small lymphocytes 92 %, large lymphocytes 2 %, promyelocytes 1 %, myelocytes 1 %, metamyelocytes 1 %, segmented neutrophils 2 %, erythroblasts 1 % She is still living—Diagnosis· *Chronic lymphogenous leukemia*

SON'S SON (County Hospital, Gentofte, service B, no 517/31)—Son of office assistant. Born at term, throve well, no exanthematous diseases When 14 months old "angina", and after that time constantly feverish, with edemas, moderate enlargement of the lymph nodes, spleen palpable 3 cm below the costal margin, hemorrhagic diathesis Hemoglobin 44 %, white cells 5,920, with 98 % of stem cells, thrombocytes 40,000 Died after about 10 weeks illness Necropsy hyperplasia of the lymphatic apparatus of the intestine, visible infiltrations in the liver, the spleen 11 × 5 × 3 cm.—Diagnosis *Stem-cell leukemia*

MOTHER'S FATHER—Died in 1889, aged 83, with a chronic facial ulcer which refused to heal and gradually had spread to one entire half of the face—Diagnosis Facial skin cancer



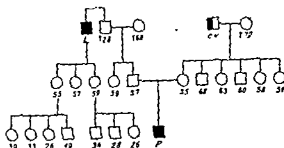
Pedigree 8

PROBAND (Norre Hospital; died June 15th, 1942).—Seamstress. Never pregnant When 18 syphilis, insufficiently treated. When 46 abrasion of uterine mucosa and roentgen castration owing to pronounced metrorrhagia. Since she was 30 chronic bronchitis, since she was 35 repeated attacks of cholelithiasis When 49 pneumonia, after which she was constantly fatigued Liver and spleen palpable 15 cm below the costal margin Hemoglobin 18 %, white cells 2,700, myeloblasts 12 %, myelocytes 2 %, staff cells 7 %, segmented neutrophils 36 %, lymphocytes 29 %, monocytes 14 %, thrombocytes 15,600 Wassermann 6, Kahn 3. The myeloblast per cent in the blood increasing to 52 % Died about 2 months after admission —Diagnosis· *Chronic myelogenous leukemia*

SISTER —Living, aged 48 When 47 years old operated on for Graves' disease at Frederiksberg Hospital, service A (no 1550/43)

COUSIN (County Hospital, Soro, died Jan 4th, 1942) —Housewife. Two childbirths When 22 angina complicated by nephritis When 46 cough, expectoration, stomatitis and fever. Hemoglobin 35 %, white cells 5,080, myeloblasts 54 %, promyelocytes 6 %, myelocytes 1 %, staff cells 2 %, segmented neutrophils 3 %, monocytes 1 %, lymphocytes 28 %, erythroblasts 5 %, thrombocytes 5,000 Wassermann negative Died two months after appearance of the first symptoms No necropsy —Diagnosis *Acute myelogenous leukemia.*

FATHER'S BROTHER —Died May 25th, 1936, aged 82 Death certificate lost. Had for several years had a chronic, growing ulcer on the lower lip Diagnosis· *Cancer of the lip*

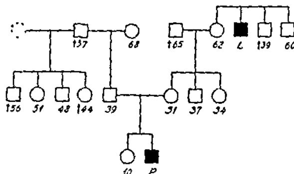


Pedigree 11

PROBAND (Municipal Hospital, service B, no. 1307/44)—Engineer Formerly well When 28 admitted on account of fatigue, pallor, loss of weight, moderate universal enlargement of lymph nodes, the spleen extending to the umbilicus Hemoglobin 30 %, white cells 107,000, nearly all lymphocytes Sternal punctate stem cells 70 %, lymphocytes 26 % Wassermann negative Duration of illness about 4 months No necropsy—Diagnosis *Stem -cell leukemia*

PATERNAL GRANDFATHER'S BROTHER (Municipal Hospital, service 2, no 1575/42)—Carpenter When 19 syphilis, well treated, when 35 abdominal typhus When 75 loss of weight, symptoms of anemia, itching of the skin and sugillations The spleen and liver palpable about 8 cm below the costal margin Hemoglobin 77 %, white cells 270,000, myeloblasts 4 %, myelocytes 22 %, metamyelocytes 4 %, staff cells 4 %, segmented neutrophils 57 %, eosinophils 4 %, lymphocytes 4 % Wassermann negative Temporarily good effect of roentgen treatment Followed for 2½ years Died in his home—Diagnosis *Chronic myelogenous leukemia*

MOTHER'S FATHER—Died May 1st, 1914, aged 63, of cancer of the stomach (death certificate)



Pedigree 10

PROBAND (Children's Hospital, Fuglebakken, no. 539/45) —Son of wholesale merchant Born at term, throve well. When 2 years old mumps, when 3 measles, when 4 whooping cough When 6 he suddenly became very pale, tired and slightly feverish, his tonsils got large and coated, there came moderate, universal enlargement of the lymph nodes, the spleen extended to the umbilicus Hemoglobin 34 %, white cells 7,680, stem cells 85 %, myelocytes 3 %, staff cells 2 %, segmented neutrophils 3 %, lymphocytes 5 %, monocytes 2 % Died after 5 weeks' illness Necropsy spleen 5 × 9 × 14 cm., leukemic infiltration in the liver, the bone marrow hyperplastic — Diagnosis *Stem-cell leukemia*

MATERNAL GRANDMOTHER'S BROTHER (Jackson Park Hospital, Chicago)*.—Wholesale merchant Formerly well When 44 years old he suddenly got indefinite pains in the lower extremities and became increasingly anemic Examination revealed systolic heart murmur, slight enlargement of the liver, but no enlargement of the spleen Hemorrhagic diathesis. Hemoglobin 30 %, white cells 4,300, small lymphocytes 45 %, large lymphocytes 35 %, segmented neutrophils 20 %, a few erythroblasts Despite repeated blood transfusions continuous bleeding from the gums Died Aug 23rd, 1929, after about 3 months illness No necropsy —Diagnosis *Acute lymphogenous leukemia*

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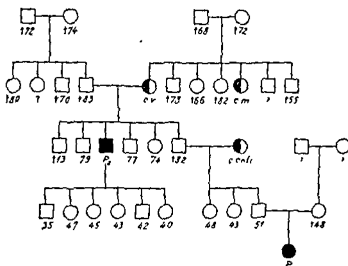
* The case history obtained by courtesy of Dr Ray *Frecark*, Chicago

Pedigree 11

PROBAND (Municipal Hospital, service B, no 1307/44) —Engineer Formerly well When 28 admitted on account of fatigue, pallor, loss of weight, moderate universal enlargement of lymph nodes, the spleen extending to the umbilicus Hemoglobin 30 %, white cells 107,000, nearly all lymphocytes Sternal punctate stem cells 70 %, lymphocytes 26 % Wassermann negative Duration of illness about 4 months No necropsy —Diagnosis *Stem-cell leukemia*

PATERNAL GRANDFATHER'S BROTHER (Municipal Hospital, service 2, no 1575/42) —Carpenter When 19 syphilis, well treated, when 35 abdominal typhus When 75 loss of weight, symptoms of anemia, itching of the skin and sugillations The spleen and liver palpable about 8 cm below the costal margin Hemoglobin 77 %, white cells 270,000, myeloblasts 4 %, myelocytes 22 %, metamyelocytes 4 %, staff cells 4 %, segmented neutrophils 57 %, eosinophils 4 %, lymphocytes 4 % Wassermann negative *Temporarily* good effect of roentgen treatment Followed for 2½ years Died in his home —Diagnosis *Chronic myelogenous leukemia*

MOTHER'S FATHER —Died May 1st, 1914, aged 63, of cancer of the stomach (death certificate)



Pedigree 12

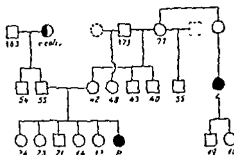
PROBAND$_1$ (County Hospital, Gentofte; service F, no. 179/43).—Secretary Never pregnant When 22 maxillary sinuitis and pneumonia. When 23 fatigue, loss of weight, moderate splenomegaly, white cells 186,800. Roentgen therapy applied with good effect When 25 spleen extending to umbilicus, hemoglobin 67 %, white cells 144,300, myeloblasts 11 %, promyelocytes 8 %, myelocytes 40 %, segmented neutrophils 20 %, eosinophils 7 %, basophils 7 %, lymphocytes 7 %. Followed for about 3 years No necropsy — Diagnosis: *Chronic myelogenous leukemia.*

FATHER'S MOTHER —Died Dec 7th, 1931, aged 61, of cancer of the sigmoid (death certificate)

PROBAND$_2$ (County Hospital, Gentofte, service F, no 527/37) —Farmer. Formerly nearly always well. When 70 enlargement of lymph nodes in the axillae and groin, later also of those in the neck Was given repeated roentgen treatments, but 4 years later the lymph nodes were again considerably enlarged, hemoglobin was 60 %, white cells 57,200, lymphocytes 93 % Observed for 4 years Died of bronchopneumonia. Necropsy leukemic infiltration in stomach, liver, spleen and lymph nodes —Diagnosis· *Chronic lymphogenous leukemia*

MOTHER —Died Dec 8th, 1905, aged 71, of cancer of the stomach (death certificate)

MOTHER'S SISTER —Died Apr 22nd, 1918, aged 75 Had for some years had a growing, ulcerating tumor in one of the breasts. The death certificate not found —Diagnosis. Cancer of the breast

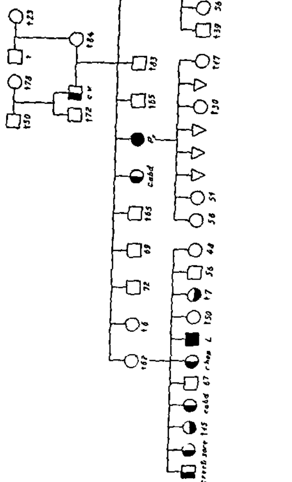


Pedigree 13

PROBAND (Queen Louise's Children's Hospital, no 936/45) —Daughter of manufacturer Born at term and seemed to get along nicely, but when 9 months old she got non-febrile convulsions and albuminuria When 20 months old she got pains in the hip and there was swelling around the joint, for which she was treated with sulfathiazole with good effect A month later there was hemorrhagic diathesis, considerable universal enlargement of the lymph nodes, the spleen extended to the umbilicus Hemoglobin 49 %, white cells 83,400, stem cells 61 %, lymphocytes 35 %, staff cells 1 %, segmented neutrophils 3 %. Died at home after about 8 weeks' illness.—Diagnosis *Stem-cell leukemia*

MOTHER'S COUSIN (Radium Center, Copenhagen; no 30291) —Housewife Two childbirths Formerly well When 34 admitted for increasing fatigue, cough and expectoration Hemoglobin 62 %, white cells 88,000, myeloblasts 8 %, myelocytes 47 %, staff cells 2 %, segmented neutrophils 36 %, basophils 2 %, lymphocytes 5 % The sternal marrow hyperplastic, with dominance of the myeloid cell type and shift towards the left in that series Wassermann negative Temporarily good effect of roentgen therapy. Observed for 2 years Still living—Diagnosis *Chronic myelogenous leukemia*

FATHER'S MOTHER —Died in the County Hospital, Næstved (no. 59/25) Jan 3rd, 1925, aged 68, of melena, after having suffered for some months from fatigue, loss of weight, and alternating diarrheas and obstipation — Diagnosis Cancer of the colon



Pedigree 14

Pedigree 14

PROBAND$_1$ (Bispebjerg Hospital, service C, no 132/10/38)—Housemaid Formerly well. Eight childbirths When 70 admitted for increasing fatigue, hen's-egg-sized lymphnodes in the axillae, liver palpable 2 cm., spleen 8 cm., below the costal margin. Hemoglobin 25 %, white cells 639,200, nearly all lymphocytes Wassermann negative. Six months later, hemoglobin 19 %, white cells 499,000, nearly all lymphocytes Followed for about 2 years No necropsy—Diagnosis Chronic lymphogenous leukemia

BROTHER (Frederiksberg Hospital, service B, no 330/25)—Factory worker When 25 rheumatic fever without complications, when 39 anal abscess When 54 admitted on account of fatigue, sudor, enlarged lymph nodes, the liver palpable 5 cm below the costal margin, the spleen to the midline and umbilicus Hemoglobin 72 %, white cells 428,000, with many myeloid cells Wassermann negative Roentgen treatment without much effect Died at home after about a year's illnes—Diagnosis Chronic myelogenous leukemia

SISTER—Died Dec 27th, 1927, aged 62, of uterine cancer (sarcomatosis) (death certificate)

FATHER—Died June 13th, 1906, aged 75, of cancer of the stomach (death certificate)

SISTER'S SON—Living, aged 69 In 1944 operated on for cancer of the rectum (Municipal Hospital, Copenhagen, service 2, no 1129/44)

SISTER'S DAUGHTER—Living, aged 68. When 58 operated on for a tumor of the breast, as large as a fist Microscopy sarcoma of the breast

SISTER'S DAUGHTER—Died May 14th, 1895, aged 15, of hemorrhagic diathesis The death certificate stated hematemesis, metrorrhagia and paresis of the lower extremities

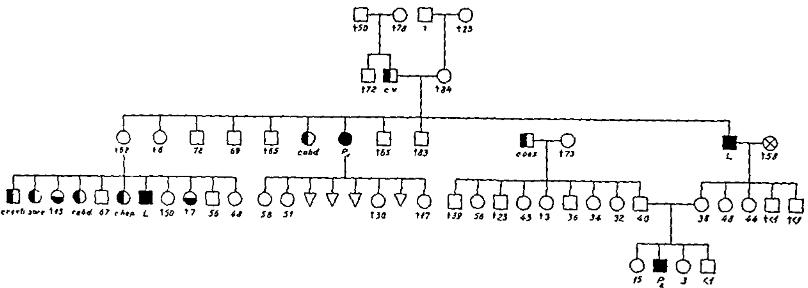
SISTER'S DAUGHTER—Died Aug 31th, 1922, aged 42, of cancer of the abdomen (death certificate)

SISTER'S DAUGHTER—Died Jan 21st, 1920, aged 33, of cancer of the liver (death certificate)

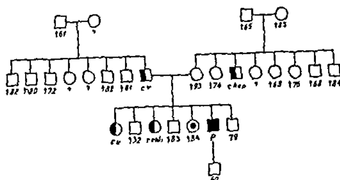
SISTER'S SON (State Hospital, service A, no 29/1/35)—Small-holder When 20 gonorrhea, without complications When 48, after a panaritium, universal enlargement of the lymph nodes, hemoglobin 71 %, white cells 126,000, 97 % of which were lymphocytes, Thrombocytes, 86,800 Followed for 18 months Died at home after about 2 years illness.—Diagnosis, Chronic lymphogenous leukemia

SISTER'S DAUGHTER—Died July 2nd, 1898, aged 7, of hemorrhagic purpura (Werlhoff's disease) (death certificate)

PROBAND$_2$ (Frederiksberg Hospital, service E, no 137/41)—Son of electrician Had had the usual exanthematous children's diseases and recurrent otitis media When 7 years old he suddenly got fever, headache and pain in the abdomen; there was no enlargement of the liver or spleen, only slight enlargement of the lymph nodes Hemoglobin falling to 60 %, white cell count varying between 50,000 and 165,000, with about 80 % of eosinophils (myelocytes 1 5 %, metamyelocytes 7 %, staff cells 7 %, transitional



Pedigree 14.



Pedigree 16

PROBAND (Bispebjerg Hospital, service B, no 58a/11/42)—Wholesale merchant. Formerly well, except for some slight symptoms of hypertrophy of the prostate When 83 he began to lose weight and to suffer from fatigue and vertigo, there were hemorrhages into the skin and up to walnut-sized lymph nodes in the neck and axillae The spleen reached nearly to the umbilicus and the iliac crest Hemoglobin 54 %, red cells 1,960,000, white cells 31,900, lymphocytes 81 %, chiefly mature forms. Wassermann negative. Roentgen treatment given with temporarily good effect, but he died 3 months after admission Necropsy (177/42) Liver 24 × 18 × 8 cm, spleen 19 × 12 × 9 cm, weighing 775 g—Diagnosis *Chronic lymphogenous leukemia*

SISTER—Died, Febr 14th, 1917, aged 67, of cancer of the uterus (death certificate)

SISTER—Died March 1st, 1939, aged 85, of cancer of the colon (death certificate)

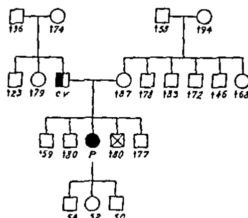
SISTER—Got struma when about 30 years old, and at the same time was nervous and got thin Died at the age of 84, of cardiac disease Diagnosis *Graves disease*

FATHER—Died Nov, 26th, 1894, aged 75, of cancer of the stomach (death certificate)

MOTHER S BROTHER—Died Oct 11th, 1877, aged 54, of cancer of the liver (death certificate)

forms 4.5 %, segmented neutrophils 58 %). Thrombocytes 171,000. Sternal punctate hyperplastic, eosinophils 56 % (promyelocytes 1 %, myelocytes 8 %, metamyelocytes 3 %, staff cells 3 %, segmented 41 %); besides, myeloblasts 1 %, promyelocytes 2 %, neutrophil myelocytes 5 %, neutrophil metamyelocytes 2 %, neutrophil staff cells 7 %, segmented neutrophils 15 %, lymphocytes 6 %, plasma cells 2 %, erythroblasts 2 %. Erythropoiesis reduced Died 11 weeks after appearance of the first symptoms Necropsy: spleen 170 g; otherwise no myeloid infiltration in the organs, but the bone marrow very rich in cells, with many eosinophile myelocytes—Diagnosis: *Eosinophilic leukemia.*

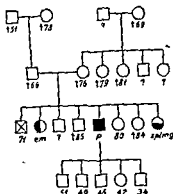
FATHER'S FATHER.—Died Sept 20th, 1935, aged 65, of cancer of the esophagus (death certificate).



Pedigree 15

PROBAND (Frederiksberg Hospital, service B, no 1836/42)—Housewife Formerly well Three childbirths When 84 she got pains in her back, when 85 pneumonia As the pain persisted, she was admitted to the hospital, where she was found to be suffering from pronounced osteomalacia of the spinal column No enlargement of liver or spleen, but hemoglobin 65 %, red cells 3,920,000, white cells 43,240, lymphocytes 93 % Wassermann negative. Died in her home 6 months later, with symptoms of severe anemia —Diagnosis *Chronic lymphogenous leukemia*

FATHER.—Died Apr 27th, 1899, aged 69, of cancer of the stomach Had during the last months before his death been suffering from anorexia and hematemeses, and had become very emaciated.

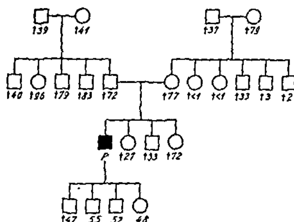


Pedigree 18

PROBAND (County Hospital, Gentofte, service B, no 228/44)—Road mender When 48 abdominal typhus When 75 admitted with lobar pneumonia, of which he eventually died Necropsy· spleen porphyrous, weighing 1240 g Liver 32 × 20 × 8 cm Lymph nodes in mesentery and hilus of the lung up to hen s-egg-sized Leukemic, lymphocytic infiltration in spleen, lymph nodes and bone marrow—Diagnosis *Chronic lymphogenous leukemia*

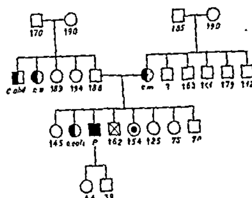
SISTER—Died 1935, aged 72, with large ulcerating tumor in one breast. —Diagnosis Breast cancer

SISTER—Died Okt. 22nd, 1909, aged 31, after 6 months' illness with increasing fatigue and growing circumference of the abdomen, splenomegaly, hemorrhagic diathesis (hematuria, purpura) and moderate enlargement of the lymph nodes Hemoglobin 54-60 %, white cells 14,200, differential count normal (State Hospital, Copenhagen, service A, no 2/10/1909) Necropsy (33/1909) High grade mitral insufficiency, with enlargement and infarction of liver and spleen No microscopy—Diagnosis Splenomegaly



Pedigree 17.

PROBAND (County Hospital, Gentofte, service C, no 1342/42) —Manufacturer When 7 scarlatina with complications from the heart; when 30 lesion of the left testis, which had to be removed When 79 admitted with symptoms of hypertrophy of the prostate Examination showed lymph gland up to hazelnut size, liver palpable 4 cm below the costal margin Hemoglobin 98 %, red cells 3,880,000, white cells 144,800, of which small lymphocytes 27 %, large lymphocytes 68 %, neutrophils 4 %, eosinophils 1 %. Sternal punctate· lymphocytes 87 %, lymphoblasts 2 %, neutrophile myelocytes 2 %, scant erythropoiesis Wassermann negative Discharged subjectively well, but with leukocytes 126,000 and hemoglobin 76 %, and died shortly afterwards at home —Diagnosis *Chronic lymphogenous leukemia*



Pedigree 20

PROBAND (Frederiksberg Hospital, service B, no 1677/43) —Bookkeeper. When 67 electro-resection of the prostate When 74 fatigue, diarrhea, increasing circumference of the abdomen, almond-sized lymph nodes in right axilla, spleen palpable 11 cm below the costal margin Hemoglobin 65 %, red cells 4,570,000, white cells 11,200, lymphocytes 45 %, monocytes 3 %, segmented neutrophils 51 %, eosinophils 1 %, thrombocytes 483,000 Sternal punctate: lymphocytes 60 % Wassermann negative Temporarily good effect of roentgen treatment Followed for 2½ years At last admission hemoglobin 52 %, white cells 4,840, lymphocytes 44 %, lymphoblasts 48 %. Died at home —*Diagnosis Chronic lymphogenous leukemia*

SISTER.—Died, Jan 20th, 1928, aged 65, of cancer of the colon (death certificate)

SISTER —Died, May 27th, 1928, aged 54, of Graves disease and cardiac disease (death certificate)

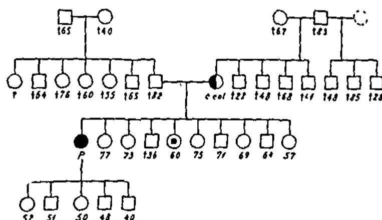
MOTHER —Died, Aug 6th, 1895, aged 62, of diabetes mellitus (death certificate), but had also for some years had an ulcerating tumor of the breast —Diagnosis Cancer of the breast

FATHER S BROTHER —Died, Sep 22nd, 1886, aged 63, of ileus (death certificate), but had already before then in remarkably short time become very emaciated and his general condition poor —Diagnosis *Cancer of the abdomen*

FATHER S SISTER —Died, Febr 2nd, 1899, aged 66, of cancer of the uterus and rectum (death certificate)

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Pedigree 19

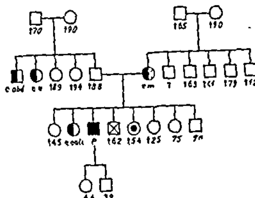


Pedigree 19

PROBAND (Bispebjerg Hospital; service B, no. 75/10/41).—Widow. Five childbirths. Always well until she, when 74 years old, got typical diabetes mellitus When 75 admitted on account of persistent diarrheas Lymph nodes everywhere bean-sized, the spleen palpable 4 cm. below the costal margin; no enlargement of the liver. Hemoglobin 99 %, red cells 5,020,000, white cells 260,000, nearly all lymphocytes Wassermann negative Roentgen therapy applied with good effect Died in her home a month after being discharged —Diagnosis· *Chronic lymphogenous leukemia*

SISTER —Living, aged 60 Formerly typical myxedema, but got thyroidin and is now well.

MOTHER —Died Apr. 10th, 1925, aged 80, of cancer of the colon (death certificate)



Pedigree 20

PROBAND (Frederiksberg Hospital; service B, no 1677/43) —Bookkeeper When 67 electro-resection of the prostate When 74 fatigue, diarrhea, increasing circumference of the abdomen, almond-sized lymph nodes in right axilla, spleen palpable 11 cm below the costal margin Hemoglobin 65 %, red cells 4 570,000, white cells 11,200, lymphocytes 45 %, monocytes 3 %, segmented neutrophils 51 %, eosinophils 1 %, thrombocytes 483,000 Sternal punctate lymphocytes 60 % Wassermann negative Temporarily good effect of roentgen treatment Followed for $2^{1}/_{2}$ years At last admission hemoglobin 52 %, white cells 4,840, lymphocytes 44 %, lymphoblasts 48 % Died at home —Diagnosis *Chronic lymphogenous leukemia*

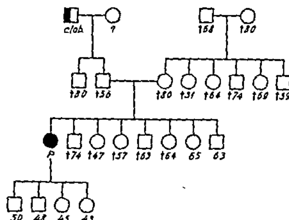
SISTER —Died, Jan 20th, 1928, aged 65, of cancer of the colon (death certificate)

SISTER —Died, May 27th, 1928, aged 54, of Graves' disease and cardiac disease (death certificate)

MOTHER —Died, Aug 6th, 1895, aged 62, of diabetes mellitus (death certificate), but had also for some years had an ulcerating tumor of the breast —Diagnosis Cancer of the breast.

FATHER'S BROTHER —Died, Sep 22nd, 1886, aged 63, of ileus (death certificate), but had already before then in remarkably short time become very emaciated and his general condition poor —Diagnosis *Cancer of the abdomen*

FATHER'S SISTER —Died, Febr 2nd, 1899, aged 66, of cancer of the uterus and rectum (death certificate)

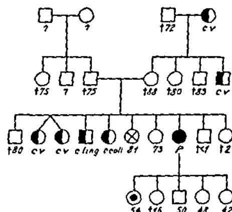


Pedigree 21.

PROBAND (Radium Center, no 20939)—Housewife Formerly well Four childbirths When 77 admitted on account of sudden extreme fatigue. Examination showed the liver palpable 5 cm. below the costal margin, the spleen reaching to the iliac crest. Hemoglobin 61 %, red cells 3,260,000, white cells 38,000, with lymphocytes 81 %; thrombocytes 32,000 Wassermann negative. Temporarily good effect of roentgen treatment. A year later, lymph node conglomerates in the neck Followed for 1 year. Died at home—Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S FATHER.—Died, aged 75 Had for some years had a growing ulcer of the lower lip—Diagnosis Cancer of the lip

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Pedigree 22

PROBAND (Bispebjerg Hospital, service C, no 98/3/1944)—Widow Formerly well Five childbirths When 72 marked fatigue, loss of weight,

night-sweats, enlargement of inguinal lymph nodes, liver palpable 4 cm below the costal margin, diminution of Traube's space. Hemoglobin 88 %, red cells 3,980,000, white cells 34,080, lymphocytes 75 %, neutrophils 24½ %, thrombocytes 270,000 Wassermann negative Good effect of roentgen treatment. Followed for about 1 year At last admission: white cells 59,000, with lymphocytes 92 % Necropsy (64/44). spleen 10 × 8 × 5 cm —Diagnosis *Chronic lymphogenous leukemia*

SISTER.—Died, Dec 12th, 1917, aged 60, of cancer of the stomach (death certificate).

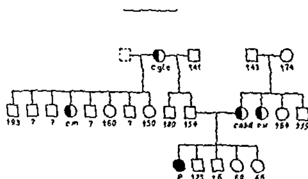
SISTER.—Died, Aug 3rd, 1935, aged 79, of cancer of the stomach (death certificate)

BROTHER.—Died, March 31st, 1904, aged 48, of cancer of the tongue (death certificate)

SISTER.—Died, May 7th, 1938, aged 79, of cancer of the colon (death certificate)

MOTHER'S BROTHER.—Died, 1880, aged 52, of cancer of the stomach, after having been confined to his bed for six months suffering from fatigue, abdominal pains an brownish vomitings

MOTHER'S MOTHER.—Died, aged 65, of cancer of the stomach, with precisely the same symptoms as in the case of the foregoing



Pedigree 23

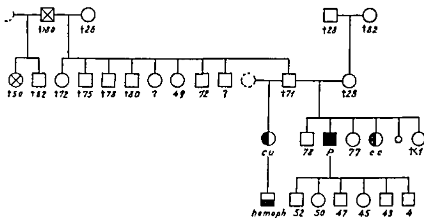
PROBAND (Frederiksberg Hospital, service C, no 261/41) —Widow. Never pregnant When 31 appendectomy When 72 enlargement of lymph nodes in neck and periodic perspiration When 74 admitted with hen's-egg-sized lymph nodes in neck, axillae and groin, hemoglobin 49 %, red cells 1,060,000, white cells 12,480, small lymphocytes 80 %, large 18 % Wassermann negative Roentgen treatment with good effect A year later blood picture unchanged Still living —Diagnosis *Chronic lymphogenous leukemia*

MOTHER.—Died, May 5th, 1906, aged 67, of cancer of the abdomen (death certificate)

MOTHER'S SISTER.—Died, Aug 21st, 1895, aged 61, of cancer of the stomach (death certificate)

FATHER'S HALF-SISTER.—Died, Oct. 25th, 1925, aged 77, of cancer of the breast (death certificate).

FATHER'S MOTHER—Died, May 27th, 1893, aged 78, of tumor in the right side of the neck (death certificate).



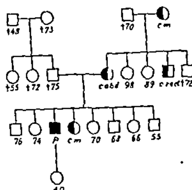
Pedigree 24

PROBAND (Frederiksberg Hospital, service B, no 1357/41)—Housewife Six childbirths Congenital heart disease Since her 60th year attacks of cholelithiasis When 71 considerable loss of weight, increasing fatigue, and gradually hemorrhages in the skin When 72 admitted for obstructive jaundice Examination showed the liver reaching to 5 cm, the spleen to 8 cm, below the costal margin, and walnut-sized lymph nodes in the neck, axillae and groin Hemoglobin 34 %, red cells 1,970,000, white cells 235,000, with lymphocytes 52 %, lymphoblasts 43 % Wassermann 3, Kahn negative Died suddenly, after 1 year's illness No necropsy—Diagnosis: *Chronic lymphogenous leukemia*

SISTER—Died, Jan 31st, 1942, 70 years old, of cancer in the cheek (death certificate)

HALF-SISTER—Died, Apr 24th, 1929, aged 45, of cancer of the uterus (death certificate)

HALF-SISTER'S SON—Living, aged 43, hemophiliac (Sundby Hospital; service M, no 443/38)



Pedigree 25

PROBAND (St. Luke s Hospital, med. service, no 384/45)—When 20 years old pneumonia Since his 70th year repeated gallstone attacks, for which he was eventually admitted No enlargement of lymph nodes, the spleen palpable 8 cm below the costal margin Hemoglobin 80 %, red cells 3,060,000, white cells 70,500, with 98 % of lymphocytes Only slight effect of roentgen treatment Still living—Diagnosis *Chronic lymphogenous leukemia*

SISTER—Died, Febr 3th, 1940, aged 55, of breast cancer (death certificate)

MOTHER—Died, Dec 2nd, 1923, aged 74, of cancer of the abdomen (death certificate)

MOTHER'S BROTHER—Died, March 23th, 1935, aged 76, of cancer of the rectum with metastases (death certificate)

MOTHER'S MOTHER—Died, about 1880, aged 71, having several times been operated on, without lasting effect, for a tumor in one of her breasts—Diagnosis Breast cancer

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Pedigree 26

PROBAND (Radium Center; no 29682) —Mail-carrier When 67 years old dyspnea and stenocardia When 68 enlargement of lymph nodes in neck and groin, accompanied by sweats and itching of the skin, increasing fatigue and dizziness; increasing circumference of the abdomen. Hemoglobin 80 %, red cells 3,950,000, white cells 12,500, with 89½ % of lymphocytes Thrombocytes 14,000 Sternal punctate: Lymphocytes 75 %, erythroblasts 11 % Wassermann negative Temporarily good effect of roentgen treatment Observed for about 18 months Necropsy (71/44)· Spleen 14 × 10 × 6 cm; moderate enlargement of the liver —Diagnosis *Chronic lymphogenous leukemia*

MOTHER —Died, about 1895, aged 64, of cancer of the uterus. Had suffered from vaginal fluor and abdominal pains, and had towards the end become very emaciated

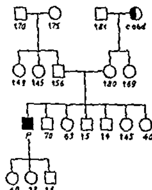
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Pedigree 27

PROBAND (State Hospital, service A, no 861/45) —Head-mistress Never pregnant. When 43 pulmonary tuberculosis, of which she was completely cured. For some years past functional dyspnea When 67 admitted for

anemia, which did not respond to iron- and liver therapy. No enlargement of liver or spleen. Hemoglobin 55 %, red cells 2,000,000, white cells 1,100, with lymphocytes 87 %, segmented neutrophils 12½ %. Sternal punctate, chiefly lymphocytes, thrombocytes 20,000. Wassermann negative. Four months later, large lymph nodes in the neck, hemoglobin 30 %, white cells 440, lymphocytes 91 %; sternal punctate: lymphocytes 87 %, chiefly small. No necropsy.—Diagnosis: *Chronic lymphogenous leukemia.*

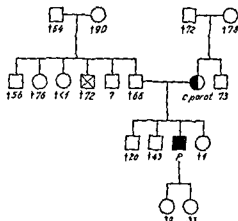
MOTHER'S FATHER.—Died, Dec. 31st, 1873, aged 56, of cancer of the abdomen, after having been in bed for about 6 months. (Abdomen large, but otherwise he was very emaciated and suffered from obstipation. No history of cardiac disease.)



Pedigree 28

PROBAND (Sundby Hospital, service M, no. 1831/42).—School-teacher. Formerly well. When 66 increasing anemia, marked, diffuse swelling of the lymph nodes. Hemoglobin 70 %, red cells 3,380,000, white cells 832,000, nearly all lymphocytes. Wassermann negative. Three admissions, in all; at the last: white cells 180,000, with 94 % of lymphocytes, the liver 3 cm, the spleen 6 cm below the costal margin. Died after at least 18 months' illness. Necropsy (296/42): Spleen 10 × 6 × 20, leukemic infiltration in lymph nodes, liver and spleen.—Diagnosis: *Chronic lymphogenous leukemia.*

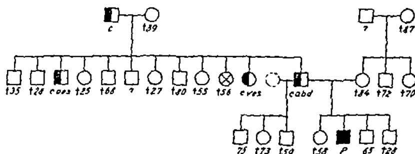
MOTHER'S MOTHER.—Died, 1827, aged 30, having been suffering from "cancer of abdomen".—Diagnosis: Abdominal cancer.



Pedigree 29.

PROBAND (Municipal Hospital, service 2, no. 1437/43) —Commercial traveller. As child diphtheria and scarlatina. When 66 fatigue, loss of weight, rises of temperature, enlargement of lymph nodes and of the spleen, which fills the whole left side of the abdomen Hemoglobin 78 %, red cells 3,800,000, white cells 185,000, lymphocytes 90 %, lymphoblasts 8 % Sternal punctate· lymphocytes 97 5 % Wassermann negative Three admissions Followed for nearly 3 years At last admission, white cells 800,000 Necropsy (629/43): Spleen 16 × 13 × 7 cm, liver 29 × 19 × 10 cm. Microscopy: typical leukemia —Diagnosis· *Chronic lymphogenous leukemia*

MOTHER —Died, Dec 7th, 1890, aged 57, of cancer of both parotid glands and the liver (death certificate)



Pedigree 30

PROBAND (Radium Center, no 37701) —Police sergeant Always in good health until he was 66, when enlargement of the lymph nodes in his neck caused him to seek medical advice Examination showed hemoglobin 109 %, red cells 5,140,000, white cells 11,880, lymphocytes 47½ %, staff cells 2 %,

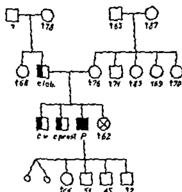
segmented neutrophils 48 %, thrombocytes 128,000 Sternal punctate: lymphocytes 40½ % Splenic punctate lymphocytes 93 % Wassermann negative Roentgen treatment given with good effect Microscopy of a lymph node showed typical lymphogenous leukemia —Diagnosis. *Chronic lymphogenous leukemia*

FATHER.—Died, Aug 12th, 1917, aged 83, of cancer of the abdomen, having a growing tumor in the latter, which obstructed the passage through the intestinal tract.

FATHER S BROTHER.—Died, June 23rd, 1897, aged 69, of cancer of the esophagus (death certificate)

FATHER S SISTER.—Died, March 21st, 1918, aged 82, of cancer of the bladder (death certificate)

FATHER S FATHER—Died, about 1880, about 70 years old, according to positive statements from cancer

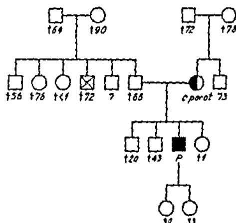


Pedigree 31

PROBAND (County Hospital, Gentofte, service F, no 1372/38)—Stoker Always in good health until he when 66 years old got pneumonia, after which time he was constantly tired and shortly afterwards was admitted with lymph nodes the size of a hen s egg in the neck, axillae and groin, and the spleen reaching to 2 cm below the costal margin Hemoglobin 90 %, red cells 3,950,000, white cells 4,980, lymphocytes 52 %, neutrophils 42½ %, eosinophils 3½ %, atypical forms 1½ % Wassermann negative Microscopy of an excised lymph node showed lymphogenous leukemia. Suddenly demanded to be discharged —Diagnosis *Chronic lymphogenous leukemia*

BROTHER —Died, Dec 8th, 1925, aged 62, of cancer of the stomach (death certificate)

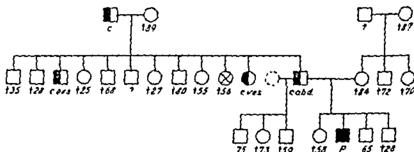
BROTHER —Living, aged 68, but suffering from cancer of the prostate,



Pedigree 29

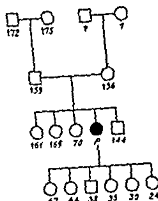
PROBAND (Municipal Hospital; service 2, no 1437/43)—Commercial traveller. As child diphtheria and scarlatina When 66 fatigue, loss of weight, rises of temperature, enlargement of lymph nodes and of the spleen, which fills the whole left side of the abdomen Hemoglobin 78 %, red cells 3,800,000, white cells 185,000, lymphocytes 90 %, lymphoblasts 8 % Sternal punctate lymphocytes 97.5 %. Wassermann negative. Three admissions Followed for nearly 3 years At last admission, white cells 800,000 Necropsy (629/43)· Spleen 16 × 13 × 7 cm, liver 29 × 19 × 10 cm Microscopy: typical leukemia.—Diagnosis· *Chronic lymphogenous leukemia.*

MOTHER—Died, Dec 7th, 1890, aged 57, of cancer of both parotid glands and the liver (death certificate)



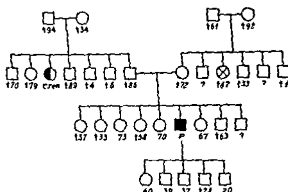
Pedigree 30

PROBAND (Radium Center, no 37701)—Police sergeant Always in good health until he was 66, when enlargement of the lymph nodes in his neck caused him to seek medical advice Examination showed hemoglobin 109 %, red cells 5,140,000, white cells 11,880, lymphocytes 47½ %, staff cells 2 %,



Pedigree 33

PROBAND (Bispebjerg Hospital, service B, no 19/9/44) —Housewife Six Childbirths When 65 admitted with pneumonia and thrombophlebitis of the right large saphenous vein Examination revealed large conglomerates of lymph nodes in axillae and groin No enlargement of liver or spleen Hemoglobin 70 %, red cells 3,320,000, white cells 79,100, small lymphocytes 7%, large lymphocytes 85 %, thrombocytes 144,000 Wassermann negative The leucocyte count rose gradually. Five months later it was 264,000, with lymphocytes 98 % Died of pulmonary embolism Necropsy (171/44): Spleen 18 × 12 × 6 cm, liver 24 × 20 × 8 cm, with leukemic infiltration – Diagnosis *Chronic lymphogenous leukemia*

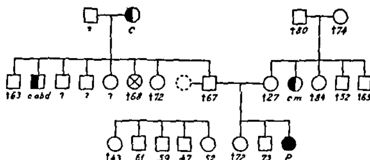


Pedigree 34

PROBAND (County Hospital, Gentofte, service C, no 1471/42) —Wholesale merchant When 29 uncomplicated gonorrhea, when 45 attack of gall-

with metastases to bones (Bispebjerg Hospital; service C. Discharged Jan 3rd, 1946)

FATHER.—Died, about 1910, aged 72, of cancer of the lip, a chronic, growing sore, which began in the lower lip.



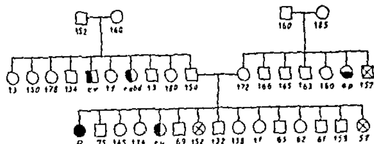
Pedigree 32.

PROBAND (Frederiksberg Hospital; service E, no. 1387/42)—Former Shop assistant Never pregnant. When 60 cholecystectomy, when 62 fracture of the humerus When 66 admitted on account of loss of weight, fatigue and itching of the skin Examination showed universal enlargement of the lymph nodes, the spleen palpable to the midline and 4 cm below the costal margin Hemoglobin 70 %, red cells 3,140,000, white cells 380,800, lymphocytes 97 %, thrombocytes 100,000. Wassermann negative Good effect of roentgen treatment Still living—Diagnosis *Chronic lymphogenous leukemia.*

MOTHER'S SISTER.—Died, Sept 30th, 1933, aged 78, of breast cancer with metastases to the liver (death certificate)

FATHER'S BROTHER—Died, about 1915, aged 68, of cancer of the abdomen. Had been suffering from vomitings and abdominal pains, and was toward the end cachectic

FATHER'S FATHER—Died, about 1873, at the age of 58, according to the family's positive statement of cancer.



Pedigree 36

PROBAND (State Hospital, service B, no 551/36) —Teacher Never pregnant After scarlet fever at the age of 12 deaf on both ears Otherwise well until she, when 65, was admitted owing to increasing fatigue, pallor and palpitations No enlargement of lymph nodes, liver or spleen Hemoglobin 43 %, red cells 1,490 000, white cells 208,800, lymphoblasts 40½ %, lymphocytes 57 % Wassermann negative Died after about 1 year's illness Necropsy (183/36) Spleen 240 g, liver 1,460 g —Diagnosis *Chronic lymphogenous leukemia*

SISTER —Died abroad, 1921, aged 47, of uterine cancer

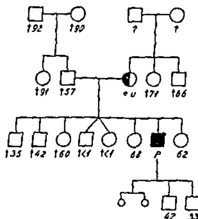
FATHER S BROTHER —Died, Nov 23rd, 1909, aged 59, of stomach cancer (death certificate)

FATHER S SISTER —Died, Dec 12th, 1853, aged 82, of abdominal cancer and ileus (death certificate)

MOTHER S SISTER —Died, Oct 18th, 1924, aged 75, of pernicious anemia (death certificate)

stone. When 65 admitted for enlarged inguinal lymph nodes Examination showed up to walnut-sized lymph nodes in the axillae and groin, and the spleen reaching to the costal margin. Hemoglobin 98 %, red cells 4,650,000, white cells 368,000, large lymphocytes 67 %, small lymphocytes 31 % Sternal punctate: lymphocytes 96 %, scant erythropoiesis. Wassermann negative Roentgen treatment was given with good effect, the leucocyte count falling to 50,000 Patient still living.—Diagnosis. *Chronic lymphogenous leukemia.*

FATHER'S SISTER.—Died, Aug 14th, 1901, aged 57, of cancer of the kidney (death certificate).



Pedigree 35

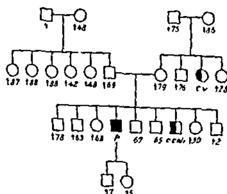
PROBAND (County Hospital, Gentofte, service B, no 1404/45).—Glazier Since his 25th year psoriasis, when 56 found to have diabetes mellitus, but *never got insulin treatment, when 64 concussion of the brain* When 65 admitted owing to night-sweats, nausea and loss of weight Examination showed the spleen extending to the costal margin, the liver to 3 cm below the latter Moderate, universal enlargement of the lymph nodes Hemoglobin 97 %, white cells 154,000, lymphoblasts 3 %, lymphocytes 95 % Sternal punctate hyperplastic lymphoblasts 11 %, lymphocytes 83 %, the erythropoiesis scant. Wassermann negative Followed for 6 months Necropsy (399/45) Spleen 600 g, many infiltrations in the liver.—Diagnosis *Chronic lymphogenous leukemia*

MOTHER.—Died, Oct 28th, 1897, aged 55, of uterine cancer (death certificate).

spleen palpable 2 cm. below the costal margin. Hemoglobin 90 %, red cells 4,920,000, white cells 48,800, lymphocytes 84½ %. Sternal punctate: lymphocytes 95.4 %, lymphoblasts 2.2 % Splenic punctate, lymphocytes 93.2 %, lymphoblasts 3.4 %. Wassermann negative Temporarily good effect of roentgen treatment. Followed for 4 years, during which the sternal punctate remained fairly unchanged Still living.—Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S BROTHER.—Died, 1888, aged 62, of abdominal cancer (death certificate)

FATHER'S BROTHER.—Died, Jan. 9th, 1901, aged 59, of stomach cancer (death certificate)



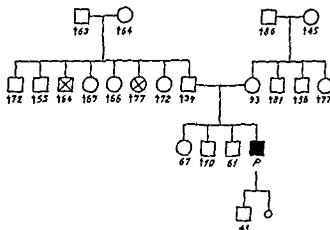
Pedigree 39

PROBAND (Frederiksberg Hospital, service B, no 1465/41).—Mail-carrier. When 40 appendectomy, when 64 suddenly high fever and a large lymph node in the neck, 6 months later liver extending to 2 cm, spleen to 3 cm, below the costal margin. Hemoglobin 82 %, red cells 3,960,000, white cells 204 000, lymphocytes 89 %, Wassermann negative Temporary good effect of roentgen treatment Still living.—Diagnosis: *Chronic lymphogenous leukemia.*

BROTHER.—Died, 1944, aged 62, of cancer of the colon (After a brief period during which he had suffered from bloody diarrheas, colostomy had been performed)

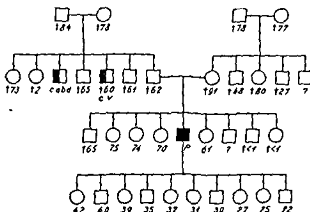
MOTHER'S SISTER.—Died, 1899, aged 52, of stomach cancer, after having suffered for several months from abdominal pains, loss of weight, fatigue and bloody vomitings

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Pedigree 37.

PROBAND (Radium Center; no 27006)—Chief electrician When 64 admitted with dry pleurisy. Examination showed several hazelnut-sized lymph nodes in neck, axillae and groin, but no enlargement of spleen or liver. No tuberculosis Hemoglobin 92 %, red cells 4,820,000, white cells 62,000, lymphocytes 91 %, neutrophils 7½ %, eosinophils ½ %, monocytes ½ %. Sternal punctate: lymphoblasts 28 3 %, lymphocytes 53 7 %, myelocytes 5 3 %, promyelocytes 1 3 %. Basal metabolism 135-129 %. Wassermann negative Temporarily good effect of roentgen treatment Still living.—Diagnosis *Chronic lymphogenous leukemia*



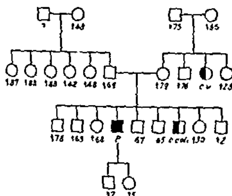
Pedigree 38

PROBAND (Radium Center, no. 29786)—Engineer When 61 he had twice a phlegmon on the right side of the neck When 64 admitted suffering from fatigue, loss of weight and enlarging lymph nodes in axillae and groin The

spleen palpable 2 cm below the costal margin Hemoglobin 90 %, red cells 4920,000, white cells 48,800, lymphocytes 84½ %. Sternal punctate: lymphocytes 95.4 %, lymphoblasts 2.2 % Splenic punctate. lymphocytes 93.2 %, lymphoblasts 3.4 % Wassermann negative. Temporarily good effect of roentgen treatment Followed for 4 years, during which the sternal punctate remained fairly unchanged Still living.—Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S BROTHER.—Died, 1888, aged 62, of abdominal cancer (death certificate)

FATHER'S BROTHER.—Died, Jan 9th, 1901, aged 59, of stomach cancer (death certificate)



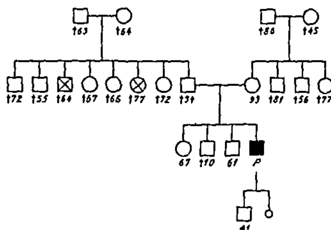
Pedigree 39

PROBAND (Frederiksberg Hospital; service B, no 1465/41) —Mail-carrier When 40 appendectomy, when 64 suddenly high fever and a large lymph node in the neck, 6 months later liver extending to 2 cm, spleen to 3 cm, below the costal margin. Hemoglobin 82 %, red cells 3,960,000, white cells 204 000, lymphocytes 89 %, Wassermann negative Temporary good effect of roentgen treatment. *Still living*.—Diagnosis *Chronic lymphogenous leukemia*.

BROTHER.—Died, 1944, aged 62, of cancer of the colon (After a brief period during which he had suffered from bloody diarrheas, colostomy had been performed)

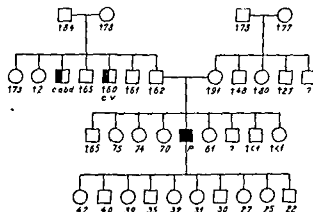
MOTHER'S SISTER.—Died, 1899, aged 52, of stomach cancer, after having suffered for several months from abdominal pains, loss of weight, fatigue and bloody vomitings

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Pedigree 37.

PROBAND (Radium Center, no 27006)—Chief electrician. When 64 admitted with dry pleurisy. Examination showed several hazelnut-sized lymph nodes in neck, axillae and groin, but no enlargement of spleen or liver. No tuberculosis Hemoglobin 92 %, red cells 4,820,000, white cells 62,000, lymphocytes 91 %, neutrophils 7½ %, eosinophils ½ %, monocytes ½ %. Sternal punctate. lymphoblasts 28.3 %, lymphocytes 53.7 %, myelocytes 5.3 %, promyelocytes 1.3 % Basal metabolism 135-129 % Wassermann negative Temporarily good effect of roentgen treatment Still living — Diagnosis: *Chronic lymphogenous leukemia*



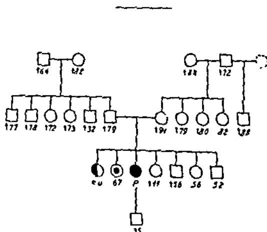
Pedigree 38

PROBAND (Radium Center, no. 29786) —Engineer When 61 he had twice a phlegmon on the right side of the neck When 64 admitted suffering from fatigue, loss of weight and enlarging lymph nodes in axillae and groin The

and left axilla. No enlargement of the spleen Hemoglobin 70 %, red cells 3,370,000, white cells 96,000, lymphocytes 98 %. Wassermann negative Died shortly after admission Necropsy (44/36): Spleen 13 × 9 × 4½ cm Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S BROTHER—Died, Sept. 4th, 1904, aged 78, of stomach cancer (death certificate)

MOTHER'S SISTER—Died, June 9th, 1913, aged 64, of ovarian cancer (death certificate)

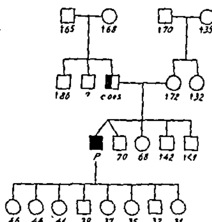


Pedigree 42

PROBAND (Radium Center, no 36642)—Housewife Three childbirths When 53 fracture of the hip When 63 admitted on account of increasing symptoms of anemia No enlargement of spleen, liver or lymph nodes Hemoglobin 100 %, red cells 4,370,000, white cells 28,360, lymphocytes 92½ %, segmented neutrophils 6½ %, thrombocytes 11,100 Wassermann negative Followed for 1 year, the blood picture unchanged Still living—Diagnosis Chronic lymphogenous leukemia.

SISTER—Died, Jan 1st, 1914, aged 29, of uterine cancer (death certificate)

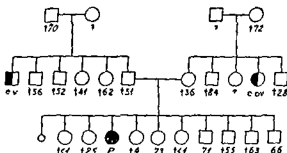
SISTER—Living, aged 67 Operated on for Graves disease (State Hospital, Copenhagen, service C, no 217/12/41)



Pedigree 40

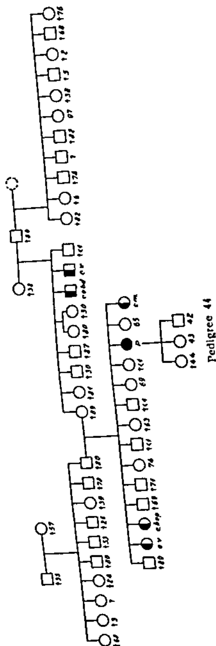
PROBAND (Frederiksberg Hospital, service B, 1353/40) —Engine-driver When 31 operation for mus articuli, when 63 operation for rupture of achilles tendon When 65 admitted with renal calculus and severe anemia Examination showed moderate, universal enlargement of the lymph nodes; the spleen extending to 5 cm below the costal margin Hemoglobin 51 %, red cells 2,580,000, white cells 343,000, lymphoblasts 4 %, lymphocytes 95½ % Wassermann negative. Temporarily good effect of roentgen treatment Followed for nearly 1 year Necropsy (389/40). Leukemic infiltration in spleen, liver, stomach and lymph nodes—Diagnosis: Chronic lymphogenous leukemia

FATHER —Died, March 5th, 1918, aged 72, of cancer of the esophagus (death certificate)



Pedigree 41.

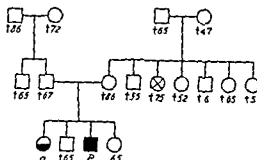
PROBAND (State Hospital, service B, no 119/36) —Teacher Never pregnant When 35 scarlatina, otherwise formerly well When 65 admitted after having suffered for 18 months from enlargement of lymph nodes in neck



Pedigree 44

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Pedigree 43



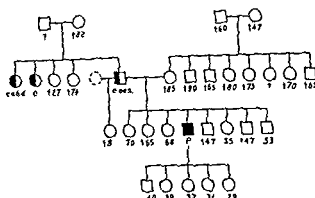
Pedigree 43.

PROBAND (Radium Center; no. 16776)—Designer. Formerly well. When 63 increasing fatigue, and shortly afterwards admitted because the lymph nodes in his neck became larger. Hemoglobin 53 %, red cells 2,860,000, white cells 154,000, lymphocytes 94½ %, lymphoblasts ½ %. Wassermann negative. Temporarily good effect of roentgen treatment. Followed for 2 years. Necropsy (36/37). Lymphogenous, leukemic infiltration in liver, kidneys, lymph nodes and bone marrow.—Diagnosis *Chronic lymphogenous leukemia*

SISTER—Died, aged 75, of macrocytic anemia (Frederiksberg Hospital; service E). When 40 Graves' disease. When 75 admitted owing to fatigue, nausea, lack of appetite and loss of weight. No glossitis or gastric achylia. Hemoglobin 34 %, color index 1.70, icterus index 15, considerable anisopoikilocytosis, besides, many macrocytes; reticulocytes 560 ‰, white blood picture normal. Necropsy: spleen 4 × 10 × 16 cm, marbled, firm, buckled. Microscopy of spleen: stasis, abundant blood pigment; of liver: *steatosis, abundant bile- or blood pigment, of bone marrow: abundant erythropoiesis.*

FATHER.—Died, Apr 29th, 1929, aged 79, of cancer of the rectum (death certificate)

FATHER S FATHER —Died, aged 52, of cancer of the stomach. (Had been unable to eat, was very emaciated, and had had many spells of vomiting)



Pedigree 46

PROBAND (Sundby Hospital, service M, no 40/40) —Foundry worker When 22 and again when 27 rheumatic fever, followed by cardiac disease When 58 admitted with hen s-egg-sized lymph nodes in neck, axillae and groin; liver 6 cm below costal margin, spleen extending to midline and to 6 cm below umbilicus Hemoglobin 58 %, red cells 2,400,000, white cells 221,000, lymphocytes 96½ %, lymphoblasts 1½ % Wassermann negative. Despite roentgen therapy the white cell count continued to rise, until it towards the end was 260,000 Necropsy (9/40) Spleen 2,800 kg, liver 34 × 32 × 7 cm, leukemic infiltration in lymph nodes, spleen and liver.—Diagnosis *Chronic lymphogenous leukemia*

FATHER —Died, June 25th, 1914, aged 67, of cancer of the esophagus (death certificate)

FATHER S SISTER —Died, about 1908, aged 78, according to the statements of several relatives, of cancer

FATHER S SISTER.—Died, July 10th, 1903, aged 65, of cancer of the abdomen (death certificate)

Pedigree 44

PROBAND (State Hospital; service P, no. 152/41).—Housewife. Three childbirths. When 4 scarlatina complicated by nephritis, when 17 again scarlatina. When 63 admitted after having been suffering for two weeks from fever, fatigue and loss of weight The spleen slightly enlarged Hemoglobin 65 %, red cells 3,120,000, white cells 3,720, lymphocytes 77 %, lymphoblasts 1½ %, monocytes 7½ %, segmented neutrophils 13½ %, basophils ½ % Sternal punctate: Lymphocytes 72 %, erythroblasts 10 %. Wassermann negative. Still living.—Diagnosis *Chronic lymphogenous leukemia.*

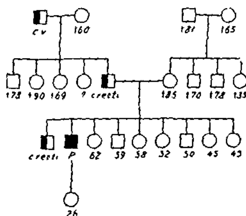
SISTER.—Died, May 9th, 1939, aged 80, of cancer of the pylorus (death certificate).

SISTER.—Died, Sept. 22nd, 1919, aged 55, of cancer of the liver (death certificate).

SISTER.—Died, June 1st, 1944, aged 58, of breast cancer (death certificate).

MOTHER'S BROTHER.—Died, Nov 10th, 1921, aged 75, of cancer of the abdomen (death certificate).

MOTHER'S BROTHER.—Died, July 5th, 1912, aged 64, of cancer of the stomach (death certificate)



Pedigree 45

PROBAND (Frederiksberg Hospital, service B, no 72/43).—Tailor When 39 severe influenza, when 60 lobar pneumonia, white cells 50,000, with lymphocytes 80 %. Wassermann negative. Blood examination five years later showed white cells 52,000, lymphocytes 2½ %, lymphocytes 87½ % Sternal punctate Lymphocytes 94 % Still living.—Diagnosis. *Chronic lymphogenous leukemia*

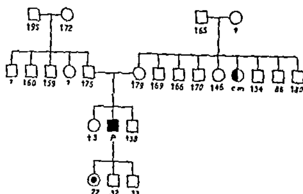
BROTHER.—Died, Dec. 19th, 1941, aged 58, of cancer of the rectum (death certificate).

Hemoglobin 39 %, red cells 1,650,000, white cells 463,000, with lymphocytes 99 %. Wassermann negative Roentgen treatment instituted, but had to be discontinued because it greatly exhausted the patient. Shortly afterwards she died at home, after at least 14 months' illness.—Diagnosis Chronic lymphogenous leukemia

FATHER'S SISTER.—Died, July 29th, 1904, aged 77, of cancer of the liver (death certificate)

FATHER'S FATHER.—Died, June 15th, 1868, aged 70, of cancer of the abdomen, was towards the end emaciated, unable to eat, and became icteric

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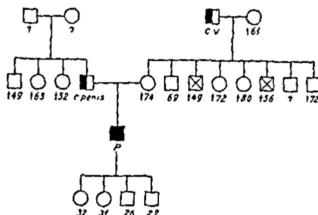
Pedigree 49

PROBAND (Radium Center, no 30235).—Waiter When 37 fracture of left tibia, when 52 hospitalised for gastric ulcer and operated on for prolapse of the rectum When 58 dyspepsia, pains under left costal margin, gradually sweats fatigue and enlargement of [illegible] globin 89 %, red cells 3,830,0[illegible] segmented neutrophils 10 %, [illegible] Temporarily good effect of roentgen treatment. [illegible] negative Followed for 3 years. Still living.—Diagnosis Chronic *lymphogenous leukemia*.

MOTHER'S SISTER.—Died, Nov 14th, 1941, aged 76, of breast cancer (death certificate)

DAUGHTER.—Living When 20 struma, exophthalmus, loss of weight, erethic Graves' disease

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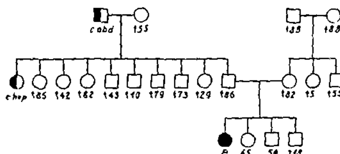


Pedigree 47.

PROBAND (Medico-legal Institute, Copenhagen).—Factory workman. When 50 cholecystectomy; in the following years stenocardia and dyspnea. When 58 severe lesion of right foot, three months later found dead in his home (Oct 20th, 1942) Necropsy· Marked enlargement of lymph nodes at root of the tongue, in the esophagus and mesentery Microscopy of liver, kidney and lymphatic apparatus of the intestine shows typical leukemic (lymphatic) infiltration —Diagnosis: *Chronic lymphogenous leukemia.*

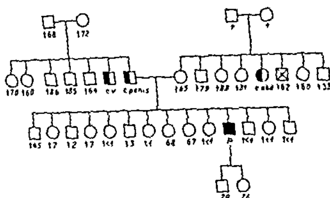
FATHER.—Died, Dec 12th, 1937, aged 78, of squamocellular carcinoma of the penis (death certificate)

MOTHER'S FATHER.—Died, Nov 15th, 1919, aged 84, of cancer of the stomach. (Towards the end emaciated, with pains in the abdomen and unable to eat).



Pedigree 48

PROBAND (Bispebjerg Hospital, service B, no. 7/10/36) —Spinster Never pregnant. When 58 increasing enlargement of lymph nodes in neck and axillae, spleen 4 cm below costal margin; rather numerous suggillations



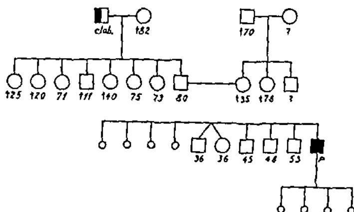
Pedigree 51

PROBAND (State Hospital, service A, no. 955/44) —Telephone workman As child uncomplicated diphtheria When 57 dyspepsia, loss of weight, enlargement of lymph nodes in axillae and groin, the spleen 8 cm below the costal margin Hemoglobin 63 %, red cells 3,120,000, white cells 89 000, lymphocytes 96 %, segmented neutrophils 3½ %, monocytes ½ % *Sternal* punctate Lymphoblasts 11 7 %, lymphocytes 82 % Splenic punctate· Lymphocytes 67 1 % Thrombocytes 126,000 Wassermann 10, Kahn 11 Still living —Diagnosis. *Chronic lymphogenous leukemia*

FATHER —Died, Aug 28th, 1925, aged 82, of squamocellular carcinoma of the penis (death certificate)

FATHER'S BROTHER.—Died, May 25th, 1895, aged 64, of cancer of the stomach (death certificate)

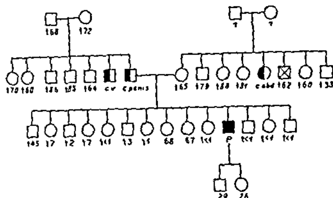
MOTHER'S SISTER.—Died, May 24th, 1925, aged 65, of cancer of the abdomen (death certificate)



Pedigree 50.

PROBAND (Radium Center; no 35711)—Van-driver Frequently bronchitis When 58 admitted owing to fatigue, loss of weight and sticking pains below left costal margin A year later, examination showed diffuse, slight enlargement of lymph nodes, spleen 5 cm, liver 8 cm, below costal margin Hemoglobin 88 %, red cells 3,930,000, white cells 24,000, lymphocytes 50 %, monocytes 3½ %, segmented neutrophils 42½ %, eosinophils ½ % Thrombocytes 121,000 Sternal punctate: Lymphocytes 69 8 %, lymphoblasts 10 7 %, Basal metabolism 175-178 % Wassermann negative After treatment with thorium X the white cell count fell to normal values (lymphocytes about 95 %), but the patient died of bronchopneumonia Necropsy Leukemic infiltration in spleen, liver and bone marrow—Diagnosis *Chronic lymphogenous leukemia*

FATHER'S FATHER—Died, aged 62, of cancer of the lip (On the lower lip, at the place where he used to hold his pipe, he had a chronic ulcer, which in his last days continued to grow larger)



Pedigree 51.

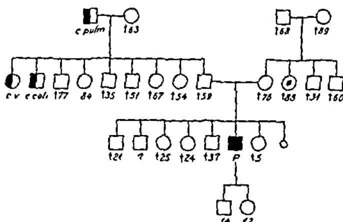
PROBAND (State Hospital, service A, no 955/44).—Telephone workman As child uncomplicated diphtheria. When 57 dyspepsia, loss of weight, enlargement of lymph nodes in axillae and groin, the spleen 8 cm. below the costal margin Hemoglobin 63 %, red cells 3,120,000, white cells 89,000, lymphocytes 96 %, segmented neutrophils 3½ %, monocytes ½ %. Sternal punctate. Lymphoblasts 11 7 %, lymphocytes 82 % Splenic punctate. Lymphocytes 67 1 % Thrombocytes 126,000 Wassermann 10, Kahn 11 Still living—Diagnosis Chronic lymphogenous leukemia

FATHER.—Died, Aug 28th, 1925, aged 82, of squamocellular carcinoma of the penis (death certificate)

FATHER'S BROTHER.—Died, May 25th, 1895, aged 64, of cancer of the stomach (death certificate)

MOTHER'S SISTER.—Died, May 24th, 1925, aged 65, of cancer of the abdomen (death certificate)

Pedigree 52



Pedigree 52

PROBAND (County Hospital, Gentofte; service B, no 1810/45).—Hairdresser. When 32 pneumonia and empyema, when 44 duodenal ulcer When 56 pneumonia twice, and when 57 again pneumonia, but the hemoglobin fell to 58 %, the white cell count rose to 171,000, with lymphocytes 94 % Sternal punctate: Lymphocytes 93 % At the same time, struma developed, which was treated with good effect with methylthiouracyl, but the blood picture remained unchanged Followed for about 1 year Still living—Diagnosis: *Chronic lymphogenous leukemia*

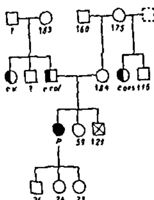
FATHER'S SISTER—Died, Jan 1st, 1924, aged 71, of cancer of the stomach (death certificate)

FATHER'S BROTHER—Died, Febr 16th, 1905, aged 48, according to the death certificate of *hemorrhoidal* tumors and *ileus*.—Diagnosis Cancer of the colon.

FATHER'S FATHER—Died, Febr 24th, 1893, aged 77, of cancer of the lung (death certificate).

MOTHER'S SISTER—Died, aged 88, of heart stroke. Had for several years been suffering from myxedema, with dry, rough skin, falling of the hair, reduced basal metabolism and loss of memory

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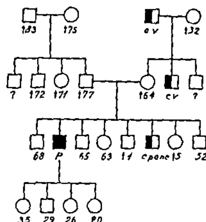
Pedigree 53

PROBAND (Bispebjerg Hospital, service B, no 11/1/42)—Housewife Three childbirths When 17 herniotomy and dilatation of the uterine cervix When 50 years phlebitis of both lower extremities When 55 bronchopneumonia. When 56, after "bronchitis", continual fatigue, fever, several attacks of gallstone Hemoglobin 58 %, red cells 2,430,000, white cells 3,100, lymphocytes 57 %, monocytes 10 %, neutrophils 33 %, thrombocytes 46,000 Sternal punctate Lymphocytes 56 %, lymphoblasts 10 %, Wassermann negative Gradually enlargement of the spleen, falling hemoglobin values and rising white cell count. Many hospitalisations, at last admission white cells 3 500, with lymphocytes 86 %. No necropsy—Diagnosis· *Chronic lymphogenous leukemia*

FATHER—Died, March 30th, 1928, aged 33, of cancer of the colon (death certificate)

FATHER'S SISTER—Died, March 25th, 1918, aged 70, of cancer of the stomach (death certificate)

MOTHER S HALF-SISTER—Died, Febr 21st, 1919, aged 75, of cancer of the esophagus (Had in the last months before death been unable to swallow solid food)



Pedigree 54

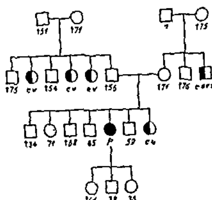
PROBAND (State Hospital; service A, no. 489/37) —Buissiness manager. Well until 56 years old, when the lymph nodes in his neck began to grow larger. At admission a year later universal enlargement of the lymph nodes to about almond-size, the spleen palpable 4 cm. below the costal margin, hemoglobin 84 %, red cells 4,600,000, white cells 367,000, lymphocytes 88 %, lymphoblasts 11 %, thrombocytes 155,000 Wassermann negative Temporarily good effect of roentgen treatment Observed for 18 months. Necropsy (149/37): Spleen 18 × 13 × 6 cm., liver 30 × 20 × 8 cm —Diagnosis *Chronic lymphogenous leukemia*

BROTHER —Died, Nov 23rd, 1943, aged 57, of cancer of the pancreas (death certificate)

MOTHER S BROTHER —Died, June 7th, 1937, aged 81, of cancer of the stomach (death certificate)

MOTHER'S FATHER.—Died, about 1897, aged 62, according to the statements of several relatives, of cancer of the stomach

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Pedigree 55

PROBAND (Radium Center, no 28721)—*Housewife* One abortion, 3 childbirths When 40 treated with iodine for Graves disease When 55 beginning enlargement of lymph nodes in the neck When 58 admitted suffering from fatigue, moderate universal enlargement of the lymph nodes, the spleen extending to 5 cm below the costal margin and 3 cm to the right of the midline Hemoglobin 84 %, red cells 4,460,000, white cells 39 000, with lymphocytes 83 % Biopsy from a lymph node showed lym-*phogenous leukemia Wassermann negative For a long time roentgen treat*ment had good effect, but gradually the white cell count rose again, there came splenomegaly, and after 4 years observation she died at home — Diagnosis Chronic lymphogenous leukemia

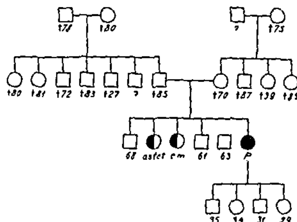
SISTER—Living, aged 58, with cancer of the uterus (Radium Center, no 24472)

FATHER S SISTER—Died, Dec 27th, 1927, aged 81, of cancer of the stomach (death certificate)

FATHER S SISTER—Died, Nov 12th, 1909, aged 78, of cancer of the stomach (death certificate)

FATHER S SISTER—Died, Sept 2nd, 1900, aged 71, of cancer of the stomach (death certificate)

MOTHER S BROTHER—Died, Aug 10th, 1922, aged 72, of cancer of the cardia (death certificate)

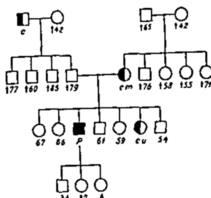


Pedigree 56.

PROBAND (Sundby Hospital; service M, no 1190/45).—Housewife. Four childbirths When 43 erythema nodosum, later dyspnea and declive edemas When 55 admitted owing to loss of weight. Examination showed moderate enlargement of lymph nodes in neck and axillae, spleen 8 cm below the costal margin Hemoglobin 95 %, red cells 4,740,000, white cells 39,600, lymphocytes 97 %, neutrophils 3 %. Sternal punctate: Lymphocytes 90 %. Wassermann negative. Temporarily good effect of roentgen treatment. Followed for 3 years. Still living—Diagnosis: *Chronic lymphogenous leukemia*

SISTER.—Died, Nov. 2nd, 1937, aged 58, in the neurologic service of the State Hospital, Copenhagen, of cervicodorsal glioma (Microscopy: Astrocytoma).

SISTER—Died, Aug. 9th, 1938, aged 60, of breast cancer (death certificate).



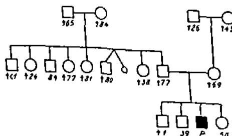
Pedigree 57.

PROBAND (Radium Center, no 18779)—Civil engineer When 41 appendectomy. When 55 admitted with large lymph nodes in the right side of the neck. *No enlargement of the spleen. Hemoglobin 94 %,* red cells 4,530,000, white cells 6,760, lymphocytes 50 % Sternal punctate· Lymphocytes 41 %, otherwise normal Wassermann negative Microscopy of a lymph node showed lymphogenous leukemia Roentgen treatment given with good effect Followed for 6 years, during which time the condition remained almost unchanged. Died of pneumonia —Diagnosis· *Chronic lymphogenous leukemia*

SISTER.—Died, Sep 25th, 1936, aged 54, of cancer of the uterus (death certificate)

MOTHER.—Died, Sep 2nd, 1930, of breast cancer (death certificate)

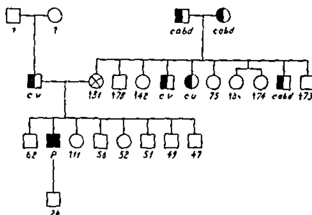
FATHER'S FATHER.—Died, Sep 29th, 1882, according to the statements of several relatives, of cancer.



Pedigree 58

PROBAND (Radium Center, no 32535)—Caterer, When 45 cholecystectomy, when 49 operation for ventral hernia When 53 hospitalised for

dyspepsia, at which time a single enlarged lymph node was found in his neck; white cells 5,000, lymphocytes 65 %. Three years later re-admitted with larger, lymph nodes in the neck, axillae and groin, spleen extending downwards into the suprapubic region. Hemoglobin 65 %, red cells 3,100,000, white cells 15,440, lymphocytes 90½ %. Sternal punctate: Lymphocytes 90 %, splenic punctate: Lymphocytes 92 %. Basal metabolic rate 170 %. Thrombocytes 54,000. Wassermann negative. Temporarily good effect of roentgen treatment Followed for about 3 years, during which time the blood picture remained more or less unchanged Still living.—Diagnosis: *Chronic lymphogenous leukemia*



Pedigree 59

PROBAND (Radium Center, no 29090) —Plumber Formerly well When 54 enlargement of the lymph nodes in neck, axillae and groin, and considerable splenomegaly Repeated hospitalisations, good effect of roentgen treatment When 58 again admitted, with large ulceration in the rhinopharynx Moderate universal enlargement of the lymph nodes, spleen extending to 8 cm., liver to 4 cm, below the costal margin Hemoglobin 63 %, red cells 3,010,000, white cells 63,200, lymphocytes 83 %, staff cells 1 %, segmented neutrophils 14½ %, monocyte 1½ % Wassermann negative Only slight effect of roentgen treatment Died at home after about 10 years' illness — Diagnosis. *Chronic lymphogenous leukemia.*

FATHER —Died, May 1st, 1905, aged 58, of stomach cancer (death certificate).

MOTHER'S BROTHER —Died, March 27th, 1922, aged 60, of stomach cancer (death certificate)

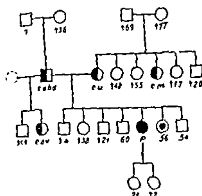
MOTHER'S SISTER —Died, Jan 9th, 1929, aged 63, of cancer of the uterus (death certificate)

MOTHER'S BROTHER —Died, 1942, aged 75, of (?) stomach cancer, metastases to the liver (Øresunds Hospital, Elsinore, no 661/41)

MOTHER'S FATHER.—Died, July 1st, 1896, aged 73, according to statements of several relatives, of cancer of the liver.

MOTHER S MOTHER.—Died, Nov 20th, 1890, aged 58, according to statements of several relatives, of cancer of the liver

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Pedigree 60

PROBAND (Frederiksberg Hospital, service E, no 192/44) —Housewife Two childbirths Since 14 migraine, when 25 pleurisy When 50 admitted owing to increasing headaches No enlargement of lymph nodes, spleen or liver Hemoglobin 85 %, red cells 3,040,000, white cells 77,400, lymphocytes 85 % Sternal punctate Lymphocytes 74¹/₂ %, lymphoblasts 3¹/₂ % Wassermann 8, Kahn 5, Meinicke strong Otherwise no symptoms of syphilis Followed for about one year No necropsy —Diagnosis *Chronic lymphogenous leukemia*

SISTER —Living, aged 56, has struma and exophthalmos, is thin, perspiring and erethic

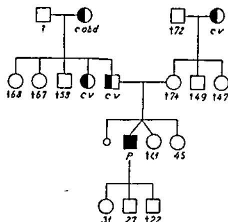
HALF-SISTER —Living, aged 70, recently operated on, in the gynecologic service of the Municipal Hospital, Copenhagen, for cancer of the left ovary

FATHER —Died, Nov 25th, 1908, aged 53, of cancer of the abdomen (death certificate)

MOTHER.—Died, Nov 9th, 1924, aged 66, of cancer of the uterus (death certificate)

MOTHER S SISTER —Died in England, aged 64, according to information of several relatives, of breast cancer

MOTHER S BROTHER —Died, Apr 2nd, 1890, aged 20, of cerebral tumor (death certificate)



Pedigree 61.

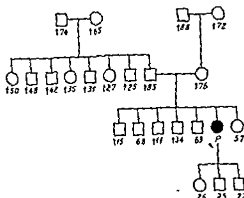
PROBAND (State Hospital; service A, no 705/9/36).—Inspector When 33 hemorrhagic colitis, when 37 severe influenza, when 51 high fever, "angina" and enlargement of lymph nodes in neck, axillae and groin, for which he was treated with roentgen When 54 admitted, with universal enlargement of the lymph nodes, spleen slightly enlarged. Hemoglobin 81 %, red cells 4,320,000, white cells 195,000, lymphocytes 90 %, lymphoblasts 8 %. Wassermann negative Renewed roentgen treatment without effect. Died two months later at home.—Diagnosis: *Chronic lymphogenous leukemia.*

FATHER.—Died, March 17th, 1903, aged 69, of cancer of the stomach (death certificate).

FATHER'S SISTER.—Died, about 1910, aged 67, of cancer of the stomach (death certificate).

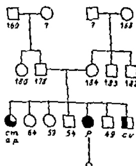
FATHER'S MOTHER.—Died, 1892, aged 72, according to statements of relatives, of cancer of the abdomen.

MOTHER'S MOTHER.—Died in the U S A, aged 68, of cancer of the stomach.



Pedigree 62.

PROBAND (State Hospital, service A, no 875/11/37)—Dentist. Three childbirths When 15 infectious hepatitis After a bronchitis when about 50, she was constantly fatigued and had periodic attacks of fever. At admission no palpable enlargement of the spleen, hemoglobin 50 %, red cells 2,560,000, white cells 4,600, lymphocytes 45 %, monocytes 2 %, segmented neutrophils 53 % Thrombocytes 162,000 Wassermann negative Sternal punctate Lymphocytes 96 % Died after at least 18 months' illness Necropsy (300/37) Spleen 300 g, leukemic infiltration in liver, kidney and lymph nodes—Diagnosis, Chronic *lymphogenous leukemia*



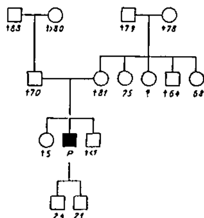
Pedigree 63

PROBAND (St Joseph's Hospital, *no* 298/42)—Housewife One childbirth When 50 marked fatigue and loss of weight, a year later admitted with severe pains across the abdomen Examination showed the spleen extending to 3 cm below the costal margin Hemoglobin 49 %, red cells

2,300,000, white cells 51,300, increasing to 82,600, nearly all large and small lymphocytes Wassermann negative Died 2 weeks after admission, about a year after the appearance of the first symptoms. No necropsy —Diagnosis: *Chronic lymphogenous leukemia.*

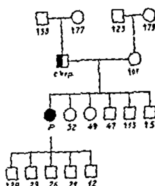
SISTER —Living, aged 69, recently operated on for breast cancer (Municipal Hospital, Aalborg; no. 2352/45) When 42 sore, athrophic tongue When 57 admitted owing to dryness of mouth and fauces, and bleedings from the rectum Hyperchromic, megalocytic anemia demonstrated (halometry 7 9 μ), color index 1.10-1.60 Specific therapy instituted with good effect When it was discontinued, paresthesias developed, but yielded to specific treatment. —Diagnosis: Pernicious anemia (Municipal Hospital, Aalborg, no. 1269/36).

BROTHER.—Died, Nov 16th, 1925, aged 38, of cancer of the stomach (death certificate).



Pedigree 64

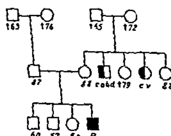
PROBAND (County Hospital, Gentofte, service F, no 1252/44) —Workingman Formerly well When 50 dry pleurisy, when 51 admitted with right-side spontaneous pneumothorax Examination showed universal enlargement of the lymph nodes, up to walnut-size, spleen 5 cm below the costal margin Hemoglobin 75 %, red cells 4,370,000, white cells 259,000, small lymphocytes 87 %, large lymphocytes 11 %, segmented neutrophils 2 % Wassermann negative No pulmonary tuberculosis No sputum Temporarily good effect of roentgen treatment Followed for 1 year Still living —Diagnosis *Chronic lymphogenous leukemia*



Pedigree 65

PROBAND (State Hospital, service A, no 194/44) — Housewife Five childbirths As child scarlatina and diphtheria, when 14 rheumatic fever with complications from the heart. When 49 fatigue, loss of weight and universal enlargement of the lymph nodes, hemoglobin 46 %, red cells 2 080 000, white cells 230 000, lymphocytes 96½ %, lymphoblasts 1½ % Thrombocytes 138 000. Wassermann negative. Temporarily good effect of roentgen treatment. Followed for 4 years Necropsy (83/44) Leukemic infiltration in lymph nodes, spleen, liver and bone marrow — Diagnosis: *Chronic lymphogenous leukemia*

FATHER — Died, Nov 28th, 1944, aged 81, of solid carcinoma of the liver (Norre Hospital, Copenhagen)



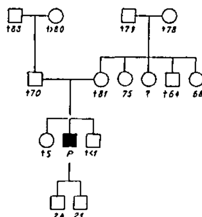
Pedigree 66

PROBAND (Municipal Hospital, service 7, no 219/45) — School-teacher Formerly well When 47 admitted for enlargement of the spleen, which on examination was found to extend almost to the midline and the iliac crest No enlargement of lymph nodes Hemoglobin 68 %, red cells 3,400,000,

2,300,000, white cells 51,300, increasing to 82,600, nearly all large and small lymphocytes Wassermann negative. Died 2 weeks after admission, about a year after the appearance of the first symptoms No necropsy —Diagnosis· *Chronic lymphogenous leukemia.*

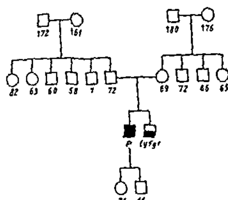
SISTER —Living, aged 69; recently operated on for breast cancer (Municipal Hospital, Aalborg; no 2352/45). When 42 sore, athrophic tongue. When 57 admitted owing to dryness of mouth and fauces, and bleedings from the rectum Hyperchromic, megalocytic anemia demonstrated (halometry 7.9 /μ), color index 1.10-1.60 Specific therapy instituted with good effect. When it was discontinued, paresthesias developed, but yielded to specific treatment —Diagnosis: Pernicious anemia (Municipal Hospital, Aalborg; no 1269/36)

BROTHER —Died, Nov 16th, 1925, aged 38, of cancer of the stomach (death certificate).



Pedigree 64

PROBAND (County Hospital, Gentofte, service F, no 1252/44) —Workingman Formerly well When 50 dry pleurisy, when 51 admitted with right-side spontaneous pneumothorax Examination showed universal enlargement of the lymph nodes, up to walnut-size; spleen 5 cm below the costal margin Hemoglobin 75 %, red cells 4,370,000, white cells 259,000, small lymphocytes 87 %, large lymphocytes 11 %, segmented neutrophils 2 % Wassermann negative No pulmonary tuberculosis No sputum Temporarily good effect of roentgen treatment Followed for 1 year Still living —Diagnosis *Chronic lymphogenous leukemia*



Pedigree 68

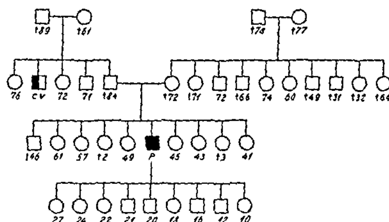
PROBAND (Radium Center, no 37475)—Timberyard workman When 10 *sanatorium treatment for enlargement of lymph nodes in the neck, since* well When 45 moderate enlargement of lymph nodes in the neck, hemoglobin 113 %, red cells 5,300,000, white cells 20,280, lymphocytes 78 %. Thrombocytes 189,000 Sternal punctate. Lymphoblasts 2 8 %, lymphocytes 77 8 % Splenic punctate Lymphocytes 86 % Wassermann negative Fairly good effect of roentgen treatment. *Still living*—*Diagnosis Chronic lymphogenous leukemia*

BROTHER (Radium Center, no 17230)—Office assistant. Formerly well. When 29 enlargement of a submaxillary lymph node, which was treated with roentgen for 2 years After that time universal enlargement of the lymph nodes No enlargement of the spleen, but increasing anemia. White cell- and differential counts normal Temporarily good effect of roentgen treatment, but died after 4½ years illness Necropsy (56/38)· Microscopy of spleen and lymph node showed typical Hodgkin's disease—Diagnosis. Malignant lymphogranulomatosis

white cells 340,000, lymphocytes 97 %. Sternal puncture: Lymphocytes 95 %. Wassermann negative Temporarily good effect of roentgen treatment, but the white cell count soon rose again. Followed for 3 years. Still living.—Diagnosis: *Chronic lymphogenous leukemia.*

MOTHER'S BROTHER.—Died, 1909, aged 61, under increasing cachexia and jaundice.—Diagnosis: Cancer of the abdomen.

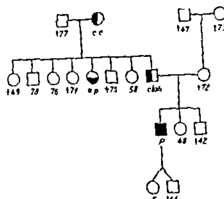
MOTHER'S SISTER.—Died, Oct 4th, 1927, of cancer of the stomach (death certificate).



Pedigree 67

PROBAND (Municipal Hospital, service 7, no 693 a/42) —Tailor. Formerly well. When 46 roentgen treatment for enlarged lymph nodes in the neck Two years later, liver extending to 3 cm, spleen to 5 cm below the costal margin Hemoglobin 42 %, red cells 1,800,000, white cells 3,100, myelocytes 7 %, monocytes 1 %, staff cells 12 %, segmented neutrophils 19 %, lymphocytes 61 % Wassermann negative Necropsy (728/42): Spleen 22 × 12 × 8 cm, leukemic infiltration in lymph nodes and bone marrow—Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S BROTHER.—Died, Nov., 1927, aged 65, of cancer of the stomach (death certificate)



Pedigree 70

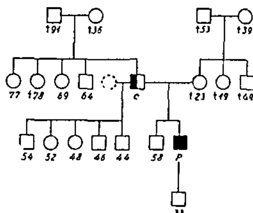
PROBAND (Sundby Hospital, service M, no 1459/41)—Ship-master. Always in good health until he, when 43, noticed enlargement of the lymph nodes in neck, axillae and groin Three years later admitted owing to fatigue Hemoglobin 94 %, red cells 4,870,000, white cells 156,000, lymphocytes 95 % *Wassermann negative Good effect of roentgen treatment* Followed for 1 month Died in his home about a year later—Diagnosis *Chronic lymphogenous leukemia*

FATHER—Died, Oct 9th, 1909, aged 49, of epithelioma of the lower lip (State Hospital, Copenhagen, service D, no 476/1907)

FATHER'S SISTER—Died, Dec 31st, 1922, aged 64, of pernicious anemia (death certificate)

FATHER'S MOTHER—Died, 1922, aged 86 Had then a large ulcer, between the breasts—Diagnosis Cancer of the skin

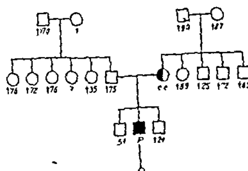
Pedigree 69



Pedigree 69.

PROBAND (Bispebjerg Hospital; service B, no 143/11/37).—Pastrycook When 30 severe influenza When 44 admitted owing to night sweats, loss of weight and pains under left costal margin Examination showed universal enlargement of lymph nodes, to hazelnut-size, the spleen extending to the right of the umbilicus and to the iliac crest. Hemoglobin 50 %, red cells 2,300,000, white cells 191,000, lymphoblasts 5 %, lymphocytes 93 % Wassermann negative. After roentgen treatment: White cell count normal, but lymphocytes 69 %, gradually hepatomegaly and severe leukocytosis Followed for 4 years No necropsy—Diagnosis *Chronic lymphogenous leukemia*

FATHER—Died, Nov. 24th, 1904, aged 42, with precisely the same pathologic picture as the proband, towards the end very large nodes in both sides of the neck The case listed as cancer

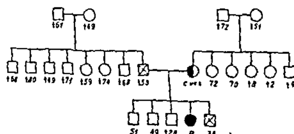


Pedigree 72

PROBAND (Radium Center, no 15401)—Manufacturer. Formerly well When 42 enlargement of lymph nodes in neck, axillae and groin, but no enlargement of spleen or liver Hemoglobin 97 %, red cells 4,890,000, white cells 12,940, lymphocytes 51 %, neutrophils 40 %, monocytes 8 %, thrombocytes 196,000 Wassermann negative Good effect of roentgen treatment Followed for 6 years The leukemia remained sub-leukemic with lymphocytes maximally 83 %, gradually increasing enlargement of the spleen Necropsy (124/43) Spleen 360 g, liver 2,550 g; leukemic infiltration in liver and lymph nodes—Diagnosis *Chronic lymphogenous leukemia*

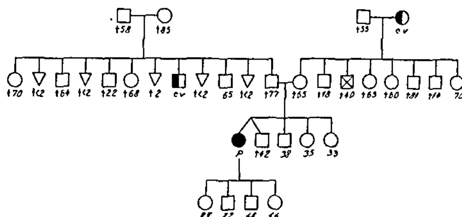
MOTHER—Living, aged 87 Has for several years had a clinically indubitable epithelioma, with elevated border, in the right temporal region —Diagnosis Cancer of the skin

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Pedigree 73

PROBAND (County Hospital, Gentofte, service F, no 346/42)—Housewife Never pregnant Formerly well When 41 large lymph nodes in neck, axillae and groin, later severe angina, increasing fatigue and loss of weight. Hemoglobin 66 %, red cells 2,870,000, white cells 18,900, with 87 % of lymphocytes Wassermann negative Temporarily good effect of roentgen

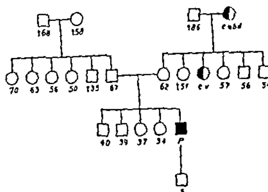


Pedigree 71.

PROBAND (Sundby Hospital, service M, no 1458/36)—Housewife. Four childbirths. Formerly well. When 42 gradual enlargement of the lymph nodes in the neck; white cells 32,600, lymphocytes 72 %. Two years later admitted with moderate universal enlargement of the lymph nodes, the spleen extending 5 cm below the costal margin, stomatitis and hemorrhagic diathesis Hemoglobin 19 %, red cells 1,100,000, white cells 28,400, nearly all lymphocytes Wassermann negative Necropsy (257/36): Hyperplasia of spleen, liver and lymph nodes.—Diagnosis. *Chronic lymphogenous leukemia.*

FATHER'S BROTHER—Died, June 3rd, 1933, aged 77, of cancer of the stomach (death certificate).

MOTHER'S MOTHER—Died, June 11th, 1921, aged 84, of cancer of the stomach (death certificate)

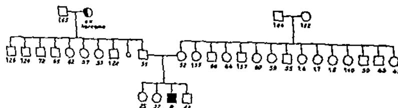


Pedigree 75

PROBAND (Municipal Hospital, service 3, no 1326/39) —Commercial agent Except for scarlatina when 19 perfectly well until he, when 21, began to suffer from fatigue, sweats and dyspnea. Later there was a sudden development of diplopia, and after extraction of a tooth continuous severe hemorrhages At admission he was very anemic His tonsils were coated and bleeding, the lymph nodes in the neck enlarged, the spleen and liver each palpable 3 cm. below the costal margin Hemoglobin 43 %, red cells 2,100,000, white cells 84,000, lymphoblasts 41 %, lymphocytes 45½ % Wassermann negative Died shortly after admission, after at least 9 months' illness Necropsy Leukemic infiltration in kidney, lymph nodes, bone marrow and spleen —Diagnosis Chronic lymphogenous leukemia

MOTHER S SISTER —Died, March 3rd, 1933, aged 38, of cancer of the stomach (death certificate)

MOTHER S MOTHER —Died, Dec 18th, 1901, of ileus (death certificate), after for some months having suffered from marked fatigue and loss of weight —Diagnosis Cancer of the abdomen

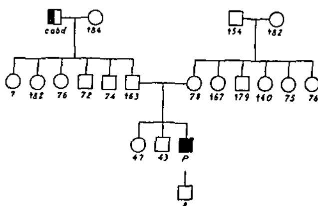


Pedigree 76

PROBAND (Frederiksberg Hospital, service E, no 924/42) —Machinist s apprentice As child tabes mesaraica, when 13 otitis media When 17 ad-

treatment. Followed until she died 9 months later. No necropsy.—Diagnosis: *Chronic lymphogenous leukemia*

MOTHER.—Died, June 5th, 1921, aged 55, of cancer of the gall-bladder (death certificate).

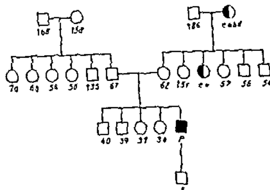


Pedigree 74

PROBAND (County Hospital, Gentofte, service C, no 572/43).—Head-clerk When 6 scarlatina, since 31 Menière's disease When 37 admitted owing to increasing fatigue, loss of weight and attacks of fever Examination showed moderate universal enlargement of the lymph nodes; no enlargement of spleen or liver Hemoglobin 48 %, red cells 1,970,000, white cells 7,440, small lymphocytes 10 %, large lymphocytes 86 %, stem-cells 3 % Thrombocytes 88,000 *Sternal punctate*· *Lymphocytes 92 %, lymphoblasts 7 %* Wassermann negative Followed for 4 weeks, during which time the white cell count rose to 38,920, with 97 % of lymphocytes Necropsy (151/43)· Spleen 15 × 10 × 4 cm, liver 27 × 24 × 10 cm—Diagnosis *Chronic lymphogenous leukemia*

FATHER S FATHER—Died, Nov 2nd, 1898, of wasting disease (verified by death certificate), after having for some months been very fatigued, with vomitings and loss of weight—Diagnosis Cancer of the abdomen

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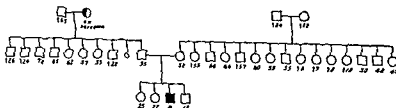
Pedigree 75

PROBAND (Municipal Hospital, service 3, no. 1326/39) —Commercial agent Except for scarlatina when 19 perfectly well until he, when 21, began to suffer from fatigue, sweats and dyspnea Later there was a sudden development of diplopia, and after extraction of a tooth continuous severe hemorrhages At admission he was very anemic. His tonsils were coated and bleeding, the lymph nodes in the neck enlarged, the spleen and liver each palpable 3 cm. below the costal margin Hemoglobin 43 %, red cells 2,100,000, white cells 64,000, lymphoblasts 41 %, lymphocytes 45½ % Wassermann negative Died shortly after admission, after at least 9 months illness Necropsy Leukemic infiltration in kidney, lymph nodes, bone marrow and spleen —Diagnosis Chronic lymphogenous leukemia

MOTHER S SISTER —Died, March 3rd, 1933, aged 38, of cancer of the stomach (death certificate)

MOTHER S MOTHER —Died, Dec 18th, 1901, of ileus (death certificate), after for some months having suffered from marked fatigue and loss of weight —Diagnosis Cancer of the abdomen

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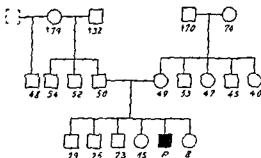


Pedigree 76

PROBAND (Frederiksberg Hospital, service E, no 924/42) —Machinist s apprentice As child tabes mesaraica, when 13 otitis media When 17 ad-

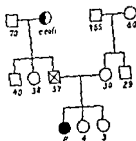
mitted with tumor of both parotid glands and serous meningitis. Hemoglobin 32 %, red cells 1,540,000, white cells 1,580, lymphoid cells 64 %. Thrombocytes 11,000 Sternal punctate: Small lymphocytes 46½ %, erythroblasts 26 %, otherwise normal. Two months later, white cells 2,080, lymphocytes 74 %, hemoglobin 46 %. Wassermann negative. Three years later highly anemic, with the spleen extending to 5 cm below the costal margin and moderate, universal enlargement of the lymph nodes.—Diagnosis: *Chronic lymphogenous leukemia*

FATHER'S MOTHER.—Died, Aug 12th, 1936, aged 83, of sarcoma of the left knee and cancer of the stomach (death certificate).



Pedigree 77

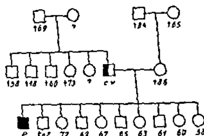
PROBAND (Sundby Hospital, service M, no. 1090/43).—Son of painter. Formerly well When 11 admitted with high fever and perspiration Examination showed tumor of lacrymal and parotid glands, tonsils large, slight universal enlargement of the lymph nodes, no enlargement of the spleen Hemoglobin 81 %, red cells 3,980,000, white cells 1,900, segmented neutrophils 4 %, lymphocytes 51 %, atypical lymphocytes 42 %, lymphoblasts 2 %, plasma cells 1 % Sternal punctate dominated by lymphocytic cells, a few normoblasts. Microscopy of a lymph node showed lymphogenous leukemia. Wassermann negative. The patient got gout and hemorrhagic diathesis. Followed for 7 months. Necropsy (147/43): Leukemic infiltration in liver, spleen, testis and bone marrow.—Diagnosis *Chronic lymphogenous leukemia.*



Pedigree 78.

PROBAND (Sundby Hospital, service F, no 27/43).—Daughter of nurseryman. Born at term, no infant's diseases, but frequent colds; when 4 again "angina" and enlargement of lymph nodes in the neck. Four months later admitted with hazelnut-sized lymph nodes in the neck, the spleen extending to the costal margin. Hardly any enlargement of the liver. Hemoglobin 62 %, red cells 3,040,000, white cells 3,300, lymphocytes 69 %, monocytes 3 %, neutrophile staff cells 7 %, segmented neutrophils 20 %, eosinophils 1 %, a single erythroblast. Sternal punctate dominated by mononuclear cells. Thrombocytes 52,000. Wassermann negative. Biopsy from a lymph node. Typical lymphogenous leukemia. Followed for 4 months. No necropsy. —Diagnosis. *Chronic lymphogenous leukemia*.

FATHER'S MOTHER.—Died, June 1941, aged 60, of cancer of the sigmoid (death certificate).

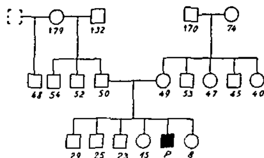


Pedigree 79

PROBAND (Municipal Hospital, service 7, no 262/45).—Former cattle dealer. When 66 operation for incarcerated hernia, when 72 herpes zoster. When 74 admitted with rectal hemorrhage. No enlargement of spleen or lymph nodes, but the liver extending 5 cm. below the costal margin. Hemoglobin 86 %, red cells 4,600,000, white cells 83,000, myeloblasts 13 %, promyelocytes 5 %, neutrophile myelocytes 17 %, neutrophile staff cells 2 %,

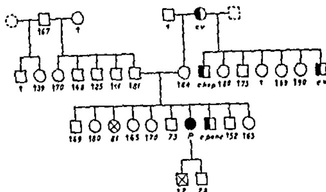
mitted with tumor of both parotid glands and serous meningitis. Hemoglobin 32 %, red cells 1,540,000, white cells 1,580, lymphoid cells 64 %. Thrombocytes 11,000. Sternal punctate: Small lymphocytes 46½ %, erythroblasts 26 %, otherwise normal. Two months later, white cells 2,080, lymphocytes 74 %, hemoglobin 46 % Wassermann negative. Three years later highly anemic, with the spleen extending to 5 cm. below the costal margin and moderate, universal enlargement of the lymph nodes—Diagnosis: *Chronic lymphogenous leukemia.*

FATHER'S MOTHER.—Died, Aug. 12th, 1936, aged 83, of sarcoma of the left knee and cancer of the stomach (death certificate).



Pedigree 77

PROBAND (Sundby Hospital, service M, no. 1090/43)—Son of painter Formerly well. When 11 admitted with high fever and perspiration Examination showed tumor of lacrymal and parotid glands, tonsils large, slight universal enlargement of the lymph nodes, no enlargement of the spleen Hemoglobin 81 %, red cells 3,980,000, white cells 1,900, segmented neutrophils 4 %, lymphocytes 51 %, atypical lymphocytes 42 %, lymphoblasts 2 %, plasma cells 1 % Sternal punctate dominated by lymphocytic cells, a few normoblasts Microscopy of a lymph node showed lymphogenous leukemia Wassermann negative The patient got gout and hemorrhagic diathesis. Followed for 7 months Necropsy (147/43): Leukemic infiltration in liver, spleen, testis and bone marrow—Diagnosis· *Chronic lymphogenous leukemia*



Pedigree 81

PROBAND (Municipal Hospital; service 2, no 459/45) —Housewife Two childbirths Always in good health until she, when 68, was admitted suffering from pains below the left costal margin There was enlargement of the spleen, which became less, however, after treatment with roentgen A year later the spleen was found occupying the entire left half of the abdomen. Hemoglobin 46 %, red cells 2,500,000, white cells 568,000, mostly promyelocytes, myelocytes and metamyelocytes, besides, a number of basophile myelocytes Wassermann negative Died 4 days after admission, of pneumonia No necropsy —Diagnosis *Chronic myelogenous leukemia*

BROTHER —Died, Sep 11th, 1930, aged 56, of cancer of the pancreas (death certificate)

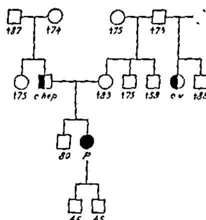
MOTHER S MOTHER —Died, July 11th, 1903, aged 86, of cancer of the stomach (death certificate)

MOTHER S HALF-BROTHER —Died, July 13th, 1917, aged 71, of cancer of the liver (death certificate)

MOTHER S HALF-BROTHER —Died, June 3rd, 1899, aged 45, of cancer of the stomach (death certificate)

segmented neutrophils 56 %, basophils 1 %, lymphocytes 6 %. Sternal punctate very rich in cells, marked shift to left in the myeloid series, slight erythropoiesis Wassermann negative. Roentgen treatment without appreciable effect. Followed for 18 months, during which time the blood picture remained more or less unchanged Still living.—Diagnosis: *Chronic myelogenous leukemia*

FATHER —Died, Jan. 30th, 1921, aged 75, of cancer of the stomach (death certificate)

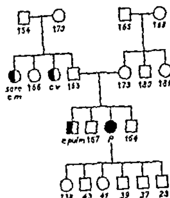


Pedigree 80

PROBAND (Municipal Hospital, service 3, no 497/41) —Widow Two childbirths Always in good health until she, when 70, began to lose weight and had pains below the left costal margin and hemorrhagic diathesis No enlargement of lymph nodes, but the spleen extending to the iliac crest and almost to the midline Hemoglobin 63 %, red cells 2,600,000, white cells 340,000, myeloblasts 9½ %, promyelocytes 16 %, neutrophile myelocytes 11 %, neutrophile metamyelocytes 14 %, neutrophile staff cells 20 %, segmented neutrophils 24 %, eosinophils 2 %, basophils 1 %, lymphocytes 2½ %. Wassermann negative Good effect of roentgen treatment Died at home after at least 1 years' illness —Diagnosis *Chronic myelogenous leukemia*

FATHER —Died, March 15th, 1895, aged 69 He had in the last year suffered from a tumor in the abdomen and became icteric shortly before death —Diagnosis Cancer of the liver

MOTHER'S HALF-SISTER —Died, Aug 30th, 1928, aged 69, of cancer of the stomach (death certificate)



Pedigree 83.

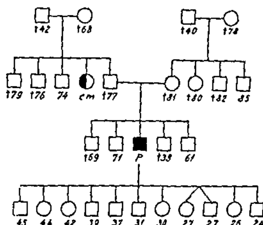
PROBAND (Radium Center; no 27277) — Housewife. Six childbirths. Formerly well When 64 increasing fatigue, dyspnea and loss of weight. Shortly afterwards herpes zoster The spleen extending to the midline and about 10 cm below the costal margin Hemoglobin 52 %, red cells 2,380,000, white cells 201,600, myeloblasts 22½ %, promyelocytes 10½ %, neutrophile myelocytes 14½ %, eosinophile myelocytes 2½ %, basophile, in all, 6 %, neutrophile metamyelocytes 11 %, neutrophile staff cells 3 %, segmented neutrophils 25½ % Sternal punctate Myeloid hyperplasia with marked shift to the left, slight erythropoiesis Thrombocytes 296,000. Wassermann negative Temporarily good effect of roentgen treatment. Followed for 3 years Necropsy (63/44) Spleen 16 × 10 × 7 cm; leukemic infiltration in spleen, liver and bone marrow — Diagnosis *Chronic myelogenous leukemia*

BROTHER — Died, Feb 8th, 1939, aged 65, of cancer of the lung (death *certificate)*

FATHER S SISTER — Died, July 14th, 1904, aged 55, of generalised sarcomatosis (death certificate) The disease had begun with a tumor in one of the breasts

FATHER S SISTER — Died, 1913, aged 67, after having been for some months confined to bed owing to great fatigue, anorexia, abdominal pains and vomitings — Diagnosis Cancer of the stomach

Pedigree 82



Pedigree 82.

PROBAND (Radium Center; no 34389)—Rentier. Formerly well. When 68 admitted owing to increasing fatigue and periodic attacks of fever. Only slight enlargement of the lymph nodes The spleen extending 6 cm. below the costal margin Hemoglobin 50 %, red cells 2,240,000, white cells 239,000, myeloblasts 7 %, promyelocytes 10 %, neutrophile myelocytes 18½ %, neutrophile metamyelocytes 9 %, neutrophile staff cells 7½ %, segmented neutrophils 34 %, eosinophils 3 %, basophils 8½ %, lymphocytes 2 %. Sternal punctate. Myeloblasts 12 %, promyelocytes 14 %, myelocytes 12 %. Thrombocytes 230,000. Basal metabolic rate 157 %. Wassermann negative Considerable effect of roentgen treatment Followed for 2 years. Still living —Diagnosis. *Chronic myelogenous leukemia*

FATHER'S SISTER—Died, March 9th, 1920, aged 54, of breast cancer (death certificate)

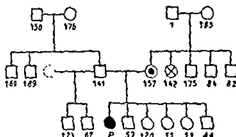
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forms Sternal puncture Normal distribution After a while hemoglobin 31 %, red cells 1,540,000, white cells 29,000, promyelocytes 1 %, neutrophile myelocytes 10 %, neutrophile metamyelocytes 7 %, neutrophile staff cells 20 %, segmented neutrophils 48 %, eosinophils 3 %, lymphocytes 16 %. Wassermann negative Discharged at own request Died shortly afterwards in his home.—Diagnosis: *Chronic myelogenous leukemia*

FATHER.—Died, Jan 18th, 1926, aged 78, of cancer of the peritoneum (primary cancer not demonstrated) (death certificate)

FATHER'S SISTER.—Died, July 17th, 1920, aged 76, of cerebral hemorrhage, but had abroad many years before been operated on for a mammary tumor, the cicatrix from the operation extending right out into the axilla.—Diagnosis Breast cancer

MOTHER'S MOTHER.—Died, Apr 27th, 1905, aged 84, *of cancer of the* colon (death certificate)

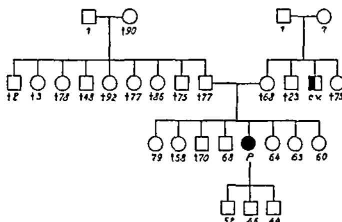


Pedigree 86.

PROBAND (Bispebjerg Hospital, service C, no 114/7/45).—Provision dealer Never *pregnant* When 30 appendectomy, when 50 bilateral iridocyclitis When 59 hospitalised for epidemic hepatitis, a month later readmitted owing to increasing fatigue Not icteric, the liver extending to 5 cm, the spleen 2 cm, below the costal margin In the left axilla a large lymph node Hemoglobin 86 % red cells 3,180 000, white cells 60,920, increasing to 110 000 myeloblasts 9 %, myelocytes 18 %, neutrophils 45 %, eosinophils 4 %, basophils 3 % lymphocytes 21 % Thrombocytes 466,000 Sternal punctate Stem cells 7 %, myeloblasts 54 %, promyelocytes 3 %, neutrophile myelocytes 6 %, neutrophile metamyelocytes 15 %, segmented neutrophils 12 % erythroblasts 3 % Wassermann negative Only brief effect of roentgen treatment Followed for 18 months Necropsy (167/45) Spleen 17 × 12 × 4 cm, liver 24 × 15 × 6½ cm.—Diagnosis: *Chronic myelogenous leukemia*

MOTHER.—Died, aged 57, of cardiac disease, had for several years had struma and exophthalmos, had been very nervous and thin, but her appetite good.—Diagnosis Graves' disease

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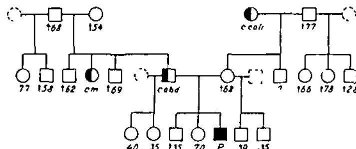


Pedigree 84

PROBAND (*Deaconesses' Hospital, service A, no. 4/42*)—*Housewife* Three childbirths Well until aged 63, when she got pneumonia followed by constant fatigue and some loss of weight When admitted 2 years later, examination showed the liver extending 4 cm below the costal margin, the spleen nearly to the umbilcal transversal, slight, non-toxic struma Hemoglobin 55 %, red cells 2,750,000, white cells 6,500, with 23 % of immature myeloid cells Wassermann negative Despite roentgen treatment, the white cell count rose to 128,600, and the hemoglobin fell to 45 % Died suddenly No necropsy—Diagnosis *Chronic myelogenous leukemia*

MOTHER'S BROTHER—Died, July 30th, 1913, aged 79, after having been confined to his bed for 2 months with bloody vomitings—Diagnosis Cancer of the stomach

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Pedigree 85

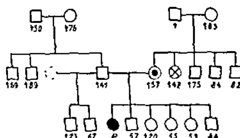
PROBAND (Sundby Hospital, service M, no 1286/42)—*Office manager* Well until he, when 62, was admitted greatly fatigued and with moderate enlargement of the spleen, white cells 16,500, with many immature cell

forms Sternal puncture Normal distribution After a while hemoglobin 31 %, red cells 1,540,000, white cells 29,000, promyelocytes 1 %, neutrophile myelocytes 10 %, neutrophile metamyelocytes 7 %, neutrophile staff cells 20 %, segmented neutrophils 48 %, eosinophils 3 %, lymphocytes 16 %. Wassermann negative Discharged at own request Died shortly afterwards in his home —Diagnosis *Chronic myelogenous leukemia.*

FATHER.—Died, Jan 18th, 1926, aged 78, of cancer of the peritoneum (primary cancer not demonstrated) (death certificate)

FATHER'S SISTER —Died, July 12th, 1920, aged 76, of cerebral hemorrhage, but had abroad many years before been operated on for a mammary tumor, the cicatrix from the operation extending right out into the axilla —Diagnosis Breast cancer

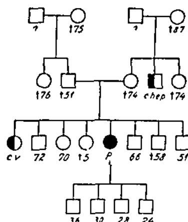
MOTHER'S MOTHER —Died, Apr 27th, 1905, aged 84, of cancer of the colon (death certificate)



Pedigree 86

PROBAND (Bispebjerg Hospital, service C, no 114/7/45) —Provision dealer Never *pregnant When 30* appendectomy, when 50 bilateral iridocyclitis When 59 hospitalised for epidemic hepatitis, a month later readmitted owing to increasing fatigue *Not icteric,* the liver extending to 5 cm., the spleen 2 cm, below the costal margin In the left axilla a large lymph node Hemoglobin 86 % red cells 3,180 000, white cells 60,920, increasing to 110 000 myeloblasts 9 %, myelocytes 18 %, neutrophils 45 %, eosinophils 4 %, basophils 3 %, lymphocytes 21 % Thrombocytes 466,000 Sternal punctate Stem cells 7 %, *myeloblasts 54 %*, promyelocytes 3 %, neutrophile myelocytes 6 %, neutrophile metamyelocytes 15 %, segmented neutrophils 12 %, erythroblasts 3 % Wassermann negative Only brief effect of roentgen treatment Followed for 18 months Necropsy (167/45) Spleen 17 × 12 × 4 cm, liver 24 × 15 × 6½ cm —Diagnosis *Chronic myelogenous leukemia*

MOTHER —Died, aged 57, of cardiac disease, had for several years had struma and exophthalmos had been *very* nervous and thin, but her appetite good —Diagnosis Graves disease

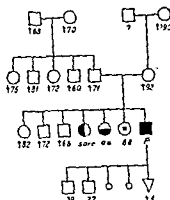


Pedigree 87

PROBAND (State Hospital, service A, no 869/44)—Housewife. Four childbirths. When 39 and a few times later cholelithiasis When 57 admitted owing to fatigue Hemoglobin 75 %, white cells 12,400, with many immature myeloid cells The spleen extending to 3 cm. below the costal margin. Three years later the spleen extended 5 cm below the umbilicus, the liver to 5 cm below the costal margin Hemoglobin 40 %, red cells 1,900,000, white cells 2,500, promyelocytes 1/2 %, myelocytes 12 %, neutrophile myelocytes 12 %, neutrophile metamyelocytes 3 1/2 %, neutrophile staff cells 5 1/2 %, segmented neutrophils 65 1/2 %, eosinophils 1/2 %, basophils 1/2 %, lymphocytes 11 %. Thrombocytes 11,000 Wassermann negative Followed for 3 years Necropsy (359/44). Spleen 3,200 g, liver 3,000 g, leukemic infiltration in spleen, liver, kidney and bone marrow—Diagnosis: *Chronic myelogenous leukemia*

SISTER—Died, Feb 2nd, 1941, aged 70, of cancer of the stomach (death certificate).

MOTHER'S BROTHER—Died, abroad, aged 35, according to the statements of several relatives he died of cancer of the liver



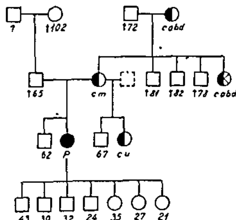
Pedigree 88

PROBAND (Bispebjerg Hospital, service B, no. 98/3/44)—Widow. Five childbirths Always in good health until she, when 57, began to suffer from fatigue Pernicious anemia was diagnosed, and she was treated for 6 years, until she, when 63, was admitted with the diagnosis of angina pectoris and cardiac disease The spleen extended 2 cm to the right of, and 3 cm. below the umbilicus, the liver 3 cm below the costal margin Hemoglobin 52 %, red cells 2,260,000, white cells 13,500, hemocytoblasts 3 %, promyelocytes 1 %, neutrophile myelocytes 22 %, neutrophile metamyelocytes 8 %, neutrophile staff cells 40 %, segmented neutrophils 14 %, lymphocytes 5 %, monocytes 1 %, Thrombocytes 272,000 Wassermann negative. Sternal punctate. Very rich in cells, with only 2 % of erythroblasts and some shift to the left in the myeloid series The splenic punctate contained many myeloid cells The patient died suddenly, of coronary thrombosis Necropsy (50/44) Spleen 27 × 13 × 8 cm, liver 31 × 24 × 9 cm—Diagnosis: *Chronic myelogenous leukemia*

SISTER—Died, Nov 16th, 1917, aged 46, of sarcoma of the pelvis (death certificate)

SISTER—Died, Aug 2nd, 1945, aged 71, of pernicious anemia ascertained already when she was 51 (color index 1.9, mean cell diameter 8.4 μ) Specific therapy had proved of good effect, but as it was not kept up myelopathies occurred Eighteen years later she was admitted to the Blegdams Hospital, Copenhagen (service B, no 645/45), hemoglobin was then 61 %, color index 1.37, white cells 4,400, mean cell diameter 7.8 μ

SISTER—Living, aged 68 Suffers from myxedema and adipositas, basal metabolism 72 % (State Hospital, Copenhagen, neuro-medical service, no 27-37)



Pedigree 89

PROBAND (Bispebjerg Hospital; service B, no 119/2/40) —Housewife Seven childbirths. When 42, and again when 50, pyelonephritis, otherwise well until at 57 admitted owing to diarrheas, loss of weight and attacks of fever No enlargement of the lymph nodes, but the spleen extending to the midline and the umbilicus Hemoglobin 78 %, red cells 4,060,000, white cells 49,600, promyelocytes 10 %, neutrophile myelocytes 29 %, neutrophile staff cells 29 %, segmented neutrophils 27 %, eosinophils 1 % Thrombocytes 276,000 Wassermann negative Temporarily good effect of roentgen treatment. Followed for 2 years Necropsy (213/40) Myeloid infiltration in liver and spleen —Diagnosis: *Chronic myelogenous leukemia*

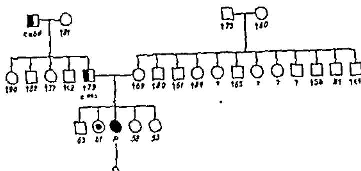
HALF-SISTER —Died, Nov 18th, 1935, aged 45, of cancer of the uterus (death certificate)

MOTHER —Died, 1894, aged 44, with an ulcerating tumor in one of her breasts —Diagnosis Mammary cancer

MOTHER'S SISTER —Died, Dec 3rd, 1936, aged 80 Had diabetes mellitus (no insulin treatment) and during her last year of life a tumor in the abdomen Died of bronchopneumonia, complicated by ileus (death certificate) —Diagnosis Cancer of the abdomen

MOTHER'S MOTHER —Died, 1880, aged 65, according to statements of relatives the death was due to cancer of the abdomen

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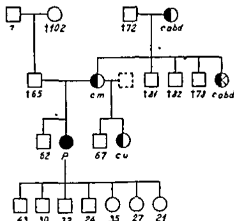
Pedigree 90

PROBAND (Deaconesses' Hospital, service C, no 1014/44) —Housewife One childbirth When 65 admitted owing to diarrheas and loss of weight. Three years later the spleen extended to the right of the midline and to the iliac crest. Hemoglobin 77 %, red cells 3,600,000, white cells 33,000, myeloblasts 4 %, promyelocytes 2 %, myelocytes 30 %, metamyelocytes 3 %, neutrophile staff cells 11 %, segmented neutrophils 37 %, erythroblasts 5 % After roentgen treatment to the spleen the white cell count showed normal values, but there were still a number of immature cells in the blood Wassermann negative Roentgen examination of the bones did not show any osteosclerosis, but in the pelvis and the lumbar vertebrae there were large destructions of bone. Roentgenologically, also the liver was enlarged. Patient still living —Diagnosis *Chronic myelogenous leukemia*

FATHER —Died, Dec 17th, 1924, aged 79, having suffered for several months from pain and difficulty when swallowing —Diagnosis. Cancer of the esophagus

FATHER'S FATHER —Died, 1881, aged 67, according to statements of several relatives, of cancer of the abdomen

SISTER —Living, aged 53 Formerly Graves disease (Had undergone a subtotal thyroidectomy at the Finsen Institute, Copenhagen, med service, no 17124)



Pedigree 89

PROBAND (Bispebjerg Hospital, service B, no 119/2/40).—Housewife Seven childbirths When 42, and again when 50, pyelonephritis, otherwise well until at 57 admitted owing to diarrheas, loss of weight and attacks of fever No enlargement of the lymph nodes, but the spleen extending to the midline and the umbilicus Hemoglobin 78 %, red cells 4,060,000, white cells 49,600, promyelocytes 10 %, neutrophile myelocytes 29 %, neutrophile staff cells 29 %, segmented neutrophils 27 %, eosinophils 1 % Thrombocytes 276,000 Wassermann negative Temporarily good effect of roentgen treatment Followed for 2 years Necropsy (213/40) Myeloid infiltration in liver and spleen —Diagnosis *Chronic myelogenous leukemia*

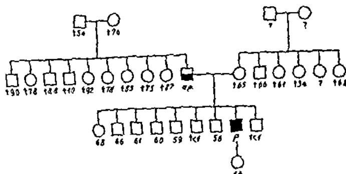
HALF-SISTER —Died, Nov 18th, 1935, aged 45, of cancer of the uterus *(death certificate)*

MOTHER —Died, 1894, aged 44, with an ulcerating tumor in one of her breasts —Diagnosis Mammary cancer

MOTHER'S SISTER —Died, Dec 3rd, 1936, aged 80 Had diabetes mellitus (no insulin treatment) and during her last year of life a tumor in the abdomen *Died of bronchopneumonia, complicated by ileus (death certificate)* —Diagnosis Cancer of the abdomen

MOTHER'S MOTHER —Died, 1880, aged 65, according to statements of relatives the death was due to cancer of the abdomen

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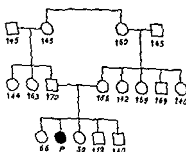


Pedigree 92

PROBAND (Frederiksberg Hospital; service Σ, no 3454/44) —Civil engineer Well until he, when 52, was admitted with pain below the left costal margin, loss of weight and night-sweats Slight universal enlargement of lymph nodes, liver extending 3 cm below the costal margin, spleen to iliac crest Hemoglobin 84 %, red cells 3,030,000, white cells 25,020, myeloblasts 15 %, promyelocytes 7 %, neutrophile myelocytes 33 %, basophile myelocytes 4 %, neutrophile staff cells 7 %, segmented neutrophile 22 %, lymphocytes 9 % Wassermann negative Good effect of roentgen treatment Still living —Diagnosis *Chronic myelogenous leukemia*

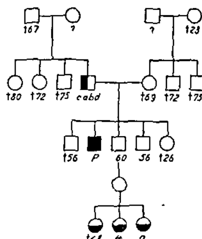
FATHER —Died, June 12th, 1915, aged 67, of pernicious anemia (St. Joseph s Hospital Copenhagen, no 96/15) Had been admitted with hemorrhagic diathesis, liver extending to 8 cm spleen to 2 cm, below the costal margin, hemoglobin 40 % a few megaloblasts in the blood. Died after gradually becoming increasingly anemic

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Pedigree 93

PROBAND (Radium Center, *no* 16320) —Housekeeper Never *pregnant* Well until she when 52 became dyspneic and began to suffer from hemorrhagic diathesis Examination showed moderate splenomegaly, red cells



Pedigree 91

PROBAND (Municipal Hospital, service 2, no 46/1/38)—Tramway employee Formerly well. When 54 admitted with pain below left costal margin, fever and rectal hemorrhage. Spleen extending to umbilicus Hemoglobin 70 %, red cells 3,500,000, white cells 75,600, neutrophile myelocytes 35 %, eosinophile myelocytes 2 %, basophile myelocytes 4 %, segmented neutrophils + neutrophile staff cells 52 % Wassermann negative Temporarily good affect of roentgen treatment Two years later again splenomegaly, white cells 110,000 Still living—Diagnosis· *Chronic myelogenous leukemia.*

FATHER.—Died, March 22nd, 1924, aged 76, of cancer of the abdomen (death certificate).

BROTHER'S GRANDCHILD—Died, Nov 17th, 1940, 11 days old, of erythroblastosis (Medico-legal institute, police section, no 14/10). Since birth very anemic, when 11 days old gasping respiration and sudden death. Necropsy showed marked anemia and moderate enlargement of spleen and liver Microscopy of the liver did not show leukemia, but lively hematopoiesis along the capillaries of the interlobular space

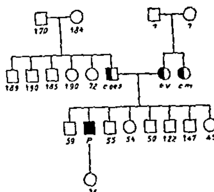
BROTHER S GRANDCHILD—Living, aged 4 In early infancy fetal erythroblastosis (discharged from the children's service of the Sundby Hospital, Sep 30th, 1941, with record of pronounced jaundice since birth, feces and urine dark, hemoglobin 66 %, red cells 2,780,000, white cells 31,200, with a number of myelocytes and erythroblasts The osmotic resistence of the erythrocytes normal Blood transfusions given with good effect)

BROTHER S GRANDCHILD—Living, 1 year old After birth very anemic (hemoglobin 67 %), but cured by iron therapy

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COUSIN—Living, aged 53 In the last three years treated for anemia (County Hospital, Varde, no 1396/43) At the beginning of treatment hemoglobin 60 %, color index 1 10, white cells 5,680, many megalocytes in the blood, besides, gastric achylia The anemia yielded to specific treatment, but there are still marked myelopathies

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Pedigree 95

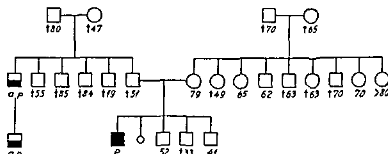
PROBAND (Bispebjerg Hospital, service C, no 24/10/42)—Furniture dealer Formerly well When 51 admitted owing to fatigue and loss of weight The spleen extending 8 cm below the costal margin Hemoglobin 74 %, red cells 3,480,000, white cells 124 000, myeloblasts 2 %, myelocytes 42 %, neutrophile staff cells 42½ %, segmented neutrophils 18½ %, eosinophils 5½ %, basophils 7½ % Sternal punctate Hyperplastic, dominated by promyelocytes Wassermann negative Temporarily good effect of roentgen treatment Followed for 2 years Necropsy (137/42) Leukemic infiltration in lymph nodes, bone marrow, liver and spleen.—Diagnosis *Chronic myelogenous leukemia*

FATHER—Died, June 9th, 1935, aged 72, of cancer of the cardia (death certificate)

MOTHER—Died, Apr 29th, 1916, aged 58, of cancer of the stomach (death certificate)

MOTHER'S SISTER—Died, 1904, aged 44, of breast *cancer (ulcerating tumor in one of the breasts)*

7,220,000, white cells 77,780, thrombocytes 48,000 Wassermann negative. Was given roentgen treatment with good effect. Two years later the spleen extended 3 cm. below and to the right of the umbilicus; hemoglobin 112 %, red cells 7,720,000, white cells 42,600, myeloblasts 4 %, promyelocytes 5 %, neutrophile myelocytes 12 %, neutrophile metamyelocytes 3 %, neutrophile staff cells 13 %, segmented neutrophils 53 %. Thrombocytes 100,000 Microscopy of bone marrow showed it highly hyperplastic, with some megacaryocytes Roentgen treatment still had good effect, but the spleen again rapidly became larger. The patient was treated once a year for 9 years During all this time the hemoglobin value remained about 100 %; the leukocyte count, though varying considerably, was as a rule below 100,000 per cmm, but always with many immature forms Roentgen examination of the bones showed normal conditions The patient is still living—Diagnosis: Chronic myelogenous leukemia (erythro-leukemia)



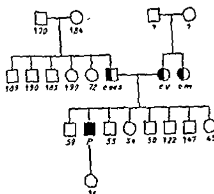
Pedigree 94

PROBAND (County Hospital, Gentofte, service C, no 1306/43)—Post-office inspector When 12 uncomplicated rheumatic fever When 51 operation for gall stone, but transferred to medical service owing to anemia. Examination showed moderate, universal enlargement of the lymph nodes, hemoglobin 60 %, red cells 2,630,000, white cells 132,000, myeloblasts 10 %, promyelocytes 23 %, neutrophile myelocytes 6 %, basophils 10 %, eosinophils 4 % Sternal punctate Myeloblasts 10 %, promyelocytes 11 %, neutrophile myelocytes 20 %, neutrophile metamyelocytes + neutrophile staff cells 24 %, segmented neutrophils 29 %. Wassermann negative Six months later admitted with hemoglobin 52 %, white cells 95,000, spleen extending 4 cm below and 5 cm to the right of the umbilicus Necropsy Liver 30 × 25 × 9 cm, spleen 26 × 18 × 10 cm—Diagnosis *Chronic myelogenous leukemia*

FATHER'S BROTHER—Died, March 3rd, 1924, aged 56, of pernicious anemia (Municipal Hospital, Horsens, no 684/23) Hemoglobin 40 %, white cells 6,000, poikilocytosis and basophil punctated erythrocytes in the blood, besides, glossitis and atrophic mucosa of the tongue

COUSIN—Living, aged 53 In the last three years treated for anemia (County Hospital, Varde, no 1396/43) At the beginning of treatment hemoglobin 60 %, color index 1 10, white cells 5,680, many megalocytes in the blood, besides, gastric achylia The anemia yielded to specific treatment, but there are still marked myelopathies

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Pedigree 95

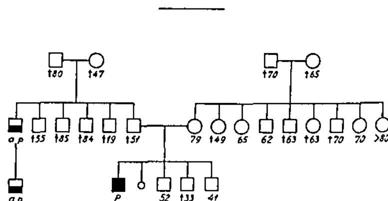
PROBAND (Bispebjerg Hospital, service C, no 24/10/42)—Furniture dealer Formerly well When *51* admitted owing to fatigue and loss of weight The spleen extending 8 cm below the costal margin. Hemoglobin 74 %, red cells 3,480,000, white cells 124,000, myeloblasts 2 %, myelocytes 42 %, neutrophile staff cells 42½ %, segmented neutrophils 18½ %, eosinophils 5½ %, basophils 7½ % Sternal punctate. Hyperplastic, dominated by promyelocytes Wassermann *negative*. *Temporarily* good effect of roentgen treatment Followed for 2 years. *Necropsy (137/42)*. Leukemic infiltration in lymph nodes, bone marrow, liver and spleen—Diagnosis· *Chronic myelogenous leukemia*

FATHER—Died, June 9th, 1935, aged 72, of cancer of the cardia (death certificate).

MOTHER—Died, Apr 29th, 1916, aged 58, of cancer of the stomach (death certificate)

MOTHER'S SISTER—Died, 1904, aged 44, of breast cancer (ulcerating tumor in one of the breasts).

7,220,000, white cells 77,780, thrombocytes 48,000 Wassermann negative Was given roentgen treatment with good effect. Two years later the spleen extended 3 cm below and to the right of the umbilicus, hemoglobin 112 %, red cells 7,720,000, white cells 42,600, myeloblasts 4 %, promyelocytes 5 %, neutrophile myelocytes 12 %, neutrophile metamyelocytes 3 %, neutrophile staff cells 13 %, segmented neutrophils 53 % Thrombocytes 100,000 Microscopy of bone marrow showed it highly hyperplastic, with some megacaryocytes Roentgen treatment still had good effect, but the spleen again rapidly became larger The patient was treated once a year for 9 years During all this time the hemoglobin value remained about 100 %, the leukocyte count, though varying considerably, was as a rule below 100,000 per cmm, but always with many immature forms Roentgen examination of the bones showed normal conditions The patient is still living —Diagnosis· *Chronic myelogenous leukemia (erythro-leukemia).*



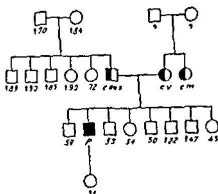
Pedigree 94

PROBAND (County Hospital, Gentofte, service C, no 1306/43) —Post-office inspector When 12 uncomplicated rheumatic fever When 51 operation for gall stone, but transferred to medical service owing to anemia Examination showed moderate, universal enlargement of the lymph nodes, hemoglobin 60 %, red cells 2,630,000, white cells 132,000, myeloblasts 10 %, promyelocytes 23 %, neutrophile myelocytes 6 %, basophils 10 %, eosinophils 4 %. Sternal punctate Myeloblasts 10 %, promyelocytes 11 %, neutrophile myelocytes 20 %, neutrophile metamyelocytes + neutrophile staff cells 24 %, segmented neutrophils 29 % Wassermann negative Six months later admitted with hemoglobin 52 %, white cells 95,000, spleen extending 4 cm below and 5 cm to the right of the umbilicus Necropsy. Liver 30 × 25 × 9 cm, spleen 26 × 18 × 10 cm —Diagnosis *Chronic myelogenous leukemia.*

FATHER S BROTHER —Died, March 3rd, 1924, aged 56, of pernicious anemia (Municipal Hospital, Horsens, no 684/23) Hemoglobin 40 %, white cells 6,000, poikilocytosis and basophil punctated erythrocytes in the blood, besides, glossitis and atrophic mucosa of the tongue

COUSIN—Living, aged 53. In the last three years treated for anemia (County Hospital, Varde, no 1396/43) At the beginning of treatment hemoglobin 60 %, color index 1 10, white cells 5,680, many megalocytes in the blood, besides, gastric achylia The anemia yielded to specific treatment, but there are still marked myelopathies

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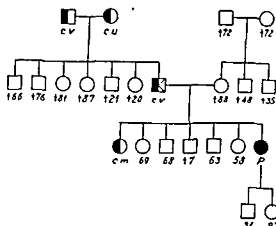
Pedigree 95

PROBAND (Bispebjerg Hospital; service C, no 24/10/42)—Furniture dealer Formerly well *When 51 admitted owing to fatigue and loss of* weight. The spleen extending 8 cm below the costal margin Hemoglobin 74 %, red cells 3,480,000, white cells 124 000, myeloblasts 2 %, myelocytes 42 %, neutrophile staff cells 42½ %, segmented neutrophils 18½ %, eosinophils 5½ %, basophils 7½ % Sternal punctate Hyperplastic, dominated by promyelocytes Wassermann negative Temporarily good effect of roentgen treatment Followed for 2 years Necropsy (137/42) Leukemic infiltration in lymph nodes, bone marrow, liver and spleen—Diagnosis *Chronic myelogenous leukemia*

FATHER—Died, June 9th, 1935, aged 72, of cancer of the cardia (death certificate)

MOTHER—Died, Apr 29th, 1916, aged 58, of cancer of the stomach (death certificate)

MOTHER'S SISTER—Died, 1904, aged 44, of breast cancer (ulcerating tumor in one of the breasts)



Pedigree 96.

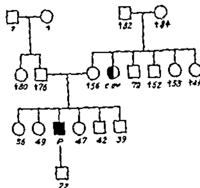
PROBAND (Radium Center, no 26596)—Widow. Two childbirths As child laryngeal diphtheria and pleurisy. When 36 myomectomy, when 38 appendectomy, when 48 concussion of the brain and fracture of three ribs Repeated excochleations of the uterus owing to hemorrhages, when 45 roentgen castration When 51 admitted owing to continuous fatigue Examination showed the spleen extending 4 cm, the liver 8 cm, below the costal margin No enlargement of lymph nodes Hemoglobin 60 %, red cells 2,760,000, white cells 419,000, myeloblasts 3½ %, neutrophile myelocytes 12½ %, neutrophile metamyelocytes 14 %, neutrophile staff cells 18½ %, segmented neutrophils 30 %, eosinophils 8 %, basophils 7½ %, lymphocytes 3 %. Wassermann negative Temporarily good effect of roentgen treatment Followed for 3 years Necropsy (105/45). Myeloid, leukemic infiltration in spleen, lymph nodes and bone marrow, spleen and liver hyperplastic — Diagnosis· *Chronic myelogenous leukemia*

SISTER—Died, June 5th, 1944, aged 69, of breast cancer (death certificate)

FATHER—Died, Dec 22nd, 1899, aged 44, of cancer of the stomach (death certificate).

FATHER'S FATHER—Died, Oct· 31st, 1890, aged 77, of cancer of the stomach (death certificate)

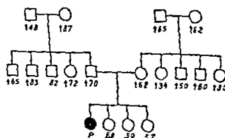
FATHER'S MOTHER—Died, Oct 5th, 1876, aged 42, of cancer of the uterus (death certificate)



Pedigree 97.

PROBAND (County Hospital, Gentofte; service F, no 206/43) —Naval officer When 27 appendectomy, when 49 increasing fatigue and eventually admitted owing to cutaneous abscesses and pallor Hemoglobin 60 %, red cells 3,000,000, white cells 3,880, of which 59 % segmented neutrophils, 40 % lymphocytes, 1 % monocytes Sternal punctate: Myeloblasts 22 %, promyelocytes 14 %, neutrophile myelocytes 32 %, Wassermann negative. Followed for nearly 3 years, now and then admitted for blood transfusion Shortly before death· Hemoglobin 41 %, white cells 9,300, myeloblasts 8 %, myelocytes 12 %, promyelocytes 17 %, lymphocytes 33 % No necropsy — Diagnosis Chronic myelogenous leukemia

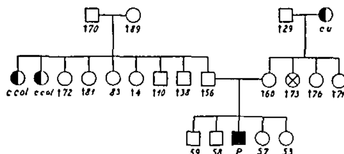
MOTHER S SISTER —Died, Sep 8th, 1920, aged 50, of cancer of the ovary (death certificate)



Pedigree 98.

PROBAND (Frederiksberg Hospital, service B, no 1215/36) —Widow. Never pregnant When 46 roentgen castration on account of severe metrorrhagia Since her 50th year repeated attacks of gout. When 51 she began to suffer from night-sweats, loss of weight, fatigue and rectal hemorrhages, and the following year she was admitted after splenomegaly had been

demonstrated. The spleen extended to the midline and to the iliac crest. Hemoglobin 55 %, red cells 3,420,000, white cells 242,800, myeloblasts 30 %, neutrophile myelocytes 48 %, neutrophile metamyelocytes 3 %, segmented neutrophils 18 %, lymphocytes 1 %. Wassermann negative Good effect of roentgen treatment Observed for 1 year. Necropsy (255/36): Spleen 29 X 17 X 8 cm —Diagnosis: *Chronic myelogenous leukemia.*



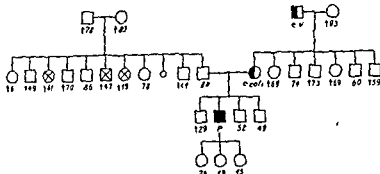
Pedigree 99.

PROBAND (County Hospital, Gentofte, service C, no 1407/45) —Housewife Never pregnant Always in excellent health until she, when 49, was admitted owing to fatigue, loss of weight and cardialgia The spleen extended 4 cm. to the right of, and 2 cm. below the umbilicus All lymph nodes about pea-sized. Hemoglobin 73 %, red cells 3,720,000, white cells 76,200, myeloblasts 4 %, myelocytes 12 %, neutrophile staff cells 12 %, segmented neutrophils 60 %, monocytes 2 % Thrombocytes 144,800 Wassermann 4, Kahn 4, gradually falling without specific treatment Temporarily good effect of roentgen treatment Seven times admitted The thyroid gland knobby and slightly enlarged. Followed for 5 years Still living —Diagnosis. *Chronic myelogenous leukemia*

FATHER'S SISTER.—Died, Apr 29th, 1913, aged 62, of cancer of the sigmoid (death certificate).

FATHER'S SISTER —Died, March 29th, 1915, aged 65 of cancer of the colon (death certificate)

MOTHER'S MOTHER —Died, June 1905, aged 74, of cancer of the uterus (death certificate)

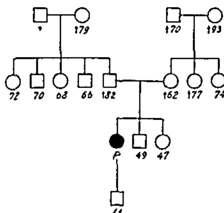


Pedigree 100

PROBAND (County Hospital, Gentofte, service B, no 1119/40)—Manufacturer Psoriasis When 30 uncomplicated gonorrhea, when 47 maxillary sinutis When 49 loss of weight and pain below left costal margin. Spleen extending 15 cm below costal margin Hemoglobin 70 %, red cells 3,100,000, white cells 170,000, myeloblasts 27 %, promyelocytes 12 %, neutrophile staff cells 20 %, segmented neutrophils 21 %, eosinophils 8 %, basophils 7 %, lymphocytes 5 % Wassermann negative Temporarily good effect of roentgen treatment Followed for 18 months. Necropsy Liver 35 × 28 × 9 cm, spleen 28 × 18 × 10 cm., myeloblastic infiltration in spleen and liver — Diagnosis: *Chronic myelogenous leukemia*

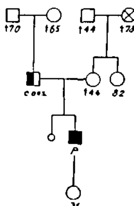
MOTHER —Died, March 17th, 1940, aged 71, of cancer of the colon (death certificate)

MOTHER'S FATHER —Died, Aug 11th, 1914, aged 70, of cancer of the stomach (death certificate)



Pedigree 101.

PROBAND (Frederiksberg Hospital; service B, no. 1073/43)—Housewife. One childbirth. When 33 uncomplicated rheumatic fever, when 42 non-specific pneumonia, when 44 roentgen castration owing to excessive menorrhagias. When 48 admitted, after pneumonia, owing to marked fatigue Examination showed the liver extending 6 cm below the costal margin, the spleen to the iliac crest and to the right of the umbilicus. Hemoglobin 73 %, white cells 299,600, myeloblasts 51 %, myelocytes 8 %, metamyelocytes 1 %, segmented neutrophils 35 %, eosinophils 1 %. Thrombocytes 594,000 Wassermann negative Followed for 3 months Necropsy (231/43): Myeloid infiltration in spleen, liver and kidneys—Diagnosis: *Chronic myelogenous leukemia.*

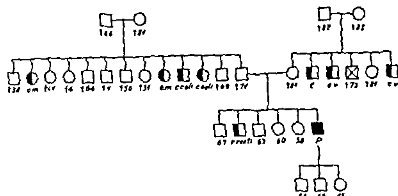


Pedigree 102

PROBAND (Municipal Hospital; service 3, no 1158/40)—Railway conductor. Well until he, when 48, was admitted owing to fatigue, edemas and

albuminuria. Universal enlargement of the lymph nodes to hazelnut-size, the spleen extending 12 cm below the costal margin. Hemoglobin 55 %, red cells 2,600,000, white cells 351,000, myeloblasts 6 %, promyelocytes 8 %, myelocytes 8 %, neutrophile metamyelocytes 26 %, neutrophile staff cells 22 %, segmented neutrophils 28 %, eosinophils 1 %, lymphocytes 1 %. Wassermann negative Followed for 6 months Died rather suddenly, in high fever No necropsy.—Diagnosis: Chronic *myelogenous leukemia*

FATHER.—Died, Feb 12th, 1904, aged 39, after suffering for 2 years from difficult deglutition and pains under the sternum.—Diagnosis: Cancer of the esophagus



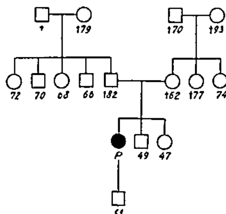
Pedigree 103

PROBAND (Bispebjerg Hospital; service B, no 165/1/39).—Naval officer. Formerly well When 47 treated abroad for fatigue and splenomegaly. Two years later admitted owing to increasing fatigue. Slight enlargement of the lymph nodes in the neck, the spleen extending 6 cm below the costal margin Hemoglobin 58 %, red cells 3,440,000, white cells 235,000, myeloblasts 52 %, neutrophile myelocytes 15 % neutrophile metamyelocytes 11 %, segmented neutrophils 17 % Wassermann negative Died suddenly of cerebral hemorrhage Necropsy (63/39) Leukemic infiltration in liver, spleen, kidneys, bone marrow, myocardium and lungs.—Diagnosis. *Chronic myelogenous leukemia*

BROTHER.—Died, July 28th, 1914, aged 34, of cancer of the rectum (death certificate).

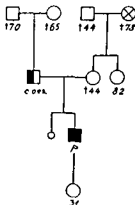
MOTHER'S BROTHER.—Died, aged 88, of cerebral apoplexy, but had, according to the statement of the family's phycisian, a deap-seated *tumor* in the abdomen

MOTHER'S BROTHER.—Died, Nov 21st, 1914, aged 76, of cancer of the stomach (death certificate)



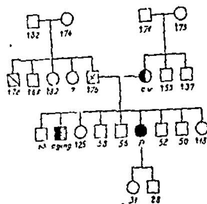
Pedigree 101.

PROBAND (Frederiksberg Hospital; service B, no. 1073/43)—Housewife One childbirth. When 33 uncomplicated rheumatic fever, when 42 non-specific pneumonia, when 44 roentgen castration owing to excessive menorrhagias. When 48 admitted, after pneumonia, owing to marked fatigue. Examination showed the liver extending 6 cm. below the costal margin, the spleen to the iliac crest and to the right of the umbilicus Hemoglobin 73 %, white cells 299,600, myeloblasts 51 %, myelocytes 8 %, metamyelocytes 1 %, segmented neutrophils 35 %, eosinophils 1 %. Thrombocytes 594,000 Wassermann negative Followed for 3 months Necropsy (231/43): Myeloid infiltration in spleen, liver and kidneys—Diagnosis: *Chronic myelogenous leukemia*



Pedigree 102

PROBAND (Municipal Hospital, service 3, no 1158/40)—Railway conductor. *Well until he, when 48, was admitted owing to fatigue,* edemas and



Pedigree 105

PROBAND (Bispebjerg Hospital, service B, no 81/I/38) —*Housewife* Two childbirths When 38 found to have pernicious anemia, for which she was treated with liver preparations with good effect When 46 "influenza", and after that time always fatigued, and her hemoglobin rate falling in spite of specific treatment, wherefore she was admitted Hemoglobin 76 %, red cells 3,520 000, white cells 80,000, myeblioblasts 12 %, promyelocytes 1 %, neutrophile staff cells 23 %, segmented neutrophils 33 %, lymphocytes 26 %, thrombocytes 99,000 Basal metabolism 137 % Wassermann negative After a while the spleen became distinctly palpable 8 cm below the costal margin Sternal punctate Promyelocytes 4 %, neutrophile myelocytes 3½ %, eosinophile myelocytes 4 %, neutrophile metamyelocytes 30 %, segmented neutrophils + staff cells 35 %, eosinophils 3 %, basophils ½ %, erythroblasts 4½ %, all normoblastic In the course of 6 months her condition got steadily worse Necropsy (93/38) Spleen 1850 g, leukemic infiltration in the kidneys —Diagnosis *Chronic myelogenous leukemia*

BROTHER —Died, Jan 21st, 1942, aged 63, of cancer of the gum (Radium Center, Copenhagen, no 23975)

MOTHER —Died, July 1st, 1928, aged 72, of cancer of the stomach (death certificate)

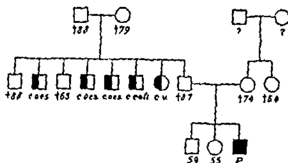
MOTHER'S BROTHER.—Died, Aug. 7th, 1925, aged 83, of cancer of the stomach (death certificate).

FATHER'S SISTER.—*Died, Apr 19th, 1880, aged 46, of breast cancer* (death certificate)

FATHER'S SISTER.—Died, Feb. 3rd, 1923, aged 77, of breast cancer (death certificate).

FATHER'S BROTHER.—Died, abroad May 2nd, 1924, aged 76, following operation for cancer of the colon.

FATHER'S SISTER.—Died, Apr 10th, 1935, aged 86, of cancer of the colon (death certificate)



Pedigree 104

PROBAND (Bispebjerg Hospital, service B, no 92/1/39).—Draper Well until he, when 47, was admitted with sticking pains in the left side and the spleen extending 5 cm below the costal margin Hemoglobin 61 %, red cells 3,830,000, white cells 214,000, myeloblasts 12 %, promyelocytes 4 %, neutrophile myelocytes 12 %, eosinophile myelocytes 4½ %, neutrophile metamyelocytes + neutrophile staff cells 29½ %, segmented neutrophils 26 %, thrombocytes 96,000 Wassermann negative Good effect of roentgen treatment Followed for 2½ years Necropsy (101/39): Leukemic infiltration in liver and kidney.—Diagnosis: *Chronic myelogenous leukemia*

FATHER'S BROTHER.—Died, July 3rd, 1938, aged 83, of cancer of the esophagus (death certificate)

FATHER'S BROTHER.—Died, May 6th, 1940, aged 79, of cancer of the *esophagus (death certificate)*

FATHER'S BROTHER.—Died, Nov 15th, 1917, aged 73, of cancer of the esophagus (death certificate)

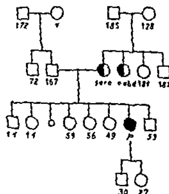
FATHER'S SISTER.—Died, May 18th, 1901, aged 57, of cancer of the stomach (death certificate)

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creasing circumference of the abdomen, sticking pains below the left costal margin When 45 admitted with slight, universal enlargement of the lymph nodes, the spleen extending 3 cm. to the right of the umbilicus and to the left iliac region. Hemoglobin 50 %, red cells 2,560,000, white cells 428,000, myeloblasts 3 %, promyelocytes 30 %, neutrophile myelocytes 19 %, neutrophile metamyelocytes 7½ %, neutrophile staff cells 6½ %, segmented neutrophils 25 %, lymphocytes 1½ %, eosinophils 4 %, basophils 3 %, thrombocytes 433,000 Wassermann negative. Sternal punctate· Hyperplastic, with shift to the left, only 1 % of erythroblasts Temporarily good effect of treatment with thorium-X. Patient still living —Diagnosis: *Chronic myelogenous leukemia*

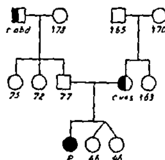
FATHER'S MOTHER —Died, June 17th, 1905, aged 77, having in the last six months been very emaciated and suffering from vomitings and abdominal pains —Diagnosis· Cancer of the stomach

MOTHER'S SISTER —Died, Nov. 23rd, 1909, aged 61, of cancer of the uterus (death certificate)



Pedigree 108.

PROBAND (Bispebjerg Hospital, service B, no. 37/1/41) —Housewife. Two childbirths When 20 abdominal operation When 44 amenorrhea and considerable loss of weight and at the same time increasing pallor Spleen extending to the midline and umbilicus Hemoglobin 54 %, red cels 2,750,000, white cells 152,000, myeloblasts 1 %, promyelocytes 11 %, neutrophile myelocytes 26 %, neutrophile staff cells 22 %, segmented neutrophils 25 %, lymphocytes 3 %, eosinophils 2 % Wassermann negative. Good effect of roentgen treatment Re-admitted 2½ years later with excessive splenomegaly and white cell count 76,000 Died shortly afterwards Necropsy· Spleen 3150 g —Diagnosis. *Chronic myelogenous leukemia*



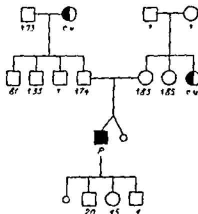
Pedigree 106

PROBAND (County Hospital, Gentofte; service B, no 669/43).—Spinster. No childbirths. When 7 scarlatina, when 20 iridocyclitis, when 38 operation for Graves' disease. When 45 increasing fatigue and pain below the left costal margin. Hemoglobin 91 %, red cells 3,560,000, white cells 141,000, myeloblasts 3 %, myelocytes 28 %, neutrophils 66 %. Wassermann negative. Temporarily good effect of roentgen treatment to the spleen, which extended to 6 cm. below the costal margin Followed for about 1 year Necropsy: Spleen 25 × 23 × 8 cm, liver 25 × 13 × 8 cm.; typical leukemic infiltration in liver, spleen and bone marrow —Diagnosis *Chronic myelogenous leukemia.*

MOTHER —Died, aged 68, according to the proband's father, who is a physician, of cancer of the gall-bladder

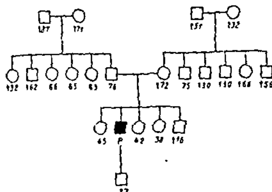
FATHER'S FATHER.—Died, aged 54, according to same source of cancer of the abdomen

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Pedigree 107

PROBAND (Radium Center, no 36288) —Small-holder When 28 pneumonia, when 44 increasing fatigue, carbuncle in the back of the neck, in-

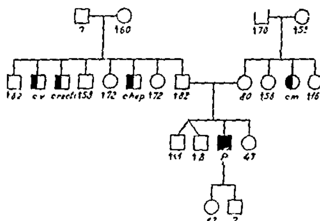


Pedigree 110

PROBAND (State Hospital, service B, no 550/38)—Head clerk When 15 infective hepatitis, since 39 repeated attacks of right-side sciatica When 43 increasing fatigue and pain in the left side of the abdomen No enlargement of lymph nodes, but the spleen extending 7 cm below the costal margin Hemoglobin 65 %, red cells 3,340,000, white cells 139,000, myeloblasts 1 %, promyelocytes 3 %, myelocytes 24 %, neutrophile metamyelocytes 10 %, neutrophile staff cells 29 %, segmented neutrophils 22 %, eosinophils 2 %, lymphocytes 3 % Wassermann negative Good effect of roentgen treatment Two month later re-admitted with high fever, white cells 8,700 myeloblasts 29 % Died after about 1 years illness Necropsy (226/38) Spleen 32 × 16 × 16 cm, liver 30 × 27 × 9 cm—Diagnosis Chronic myelogenous leukemia

MOTHER.—Died, Oct 24th, 1909, aged 53, of melanosarcoma of the cheek (death certificate).

MOTHER'S SISTER—Died, July 6th, 1911, aged 52, of cancer of the abdomen (death certificate)



Pedigree 109

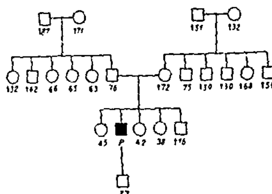
PROBAND (Municipal Hospital, service 3, no 388/44)—Mechanic. Formerly well When 43 admitted with pneumonia, in connexion with which a blood disease was demonstrated After being well for about 3 years he was again admitted, owing to increasing fatigue Examination now showed the spleen extending 10 cm below the costal margin, hemoglobin 28 %, red cells 1,800,000, white cells 210,000, myeloblasts 10 %, myelocytes 36 %, neutrophile staff cells 9 %, segmented neutrophils 42 %, lymphocytes 1 % Died shortly after admission No necropsy—Diagnosis *Chronic myelogenous leukemia*

FATHER'S BROTHER—Died, April 1905, aged 61, of cancer of the stomach (death certificate)

FATHER'S BROTHER—Died, May 12th, 1918, aged 67, of cancer of the rectum (death certificate)

FATHER'S BROTHER—Died, July 11th, 1925, aged 69, of cancer of the liver (death certificate)

MOTHER'S SISTER—Living, aged 76 May 6th, 1936, operated on for breast cancer, in the policlinic of the State Hospital, Copenhagen (The case record lost)

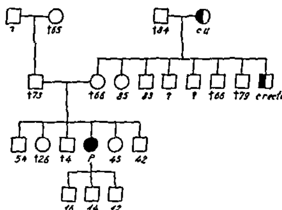


Pedigree 110

PROBAND (State Hospital, service B, no 550/38)—Head clerk. When 15 infective hepatitis, since 39 repeated attacks of right-side sciatica When 43 increasing fatigue and pain in the left side of the abdomen No enlargement of lymph nodes, but the spleen extending 7 cm below the costal margin Hemoglobin 65 %, red cells 3,340,000, white cells 139,000, myeloblasts 1 %, promyelocytes 3 %, myelocytes 24 %, neutrophile metamyelocytes 10 %, neutrophile staff cells 29 %, segmented neutrophils 22 %, eosinophils 2 %, lymphocytes 3 % Wassermann negative Good effect of roentgen treatment. Two month later re-admitted with high fever, white cells 8,700, myeloblasts 29 % Died after about 1 years' illness Necropsy (226/38). Spleen 32 × 16 × 16 cm, liver 30 × 27 × 9 cm—Diagnosis: Chronic myelogenous leukemia

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Pedigree 111

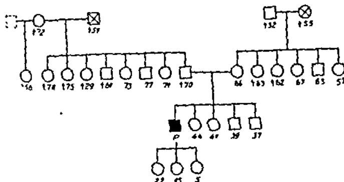


Pedigree 111.

PROBAND (Frederiksberg Hospital, service E, no 3242/44).—Housewife. Three childbirths. When 17 appendectomy, when 24 operation for abdominal inflammation, when 37 umbilical herniotomy Since her 43rd year a few attacks of gallstone. When admitted, at 46, with a view to cholecystectomy, examination showed hemoglobin 60 %, red cells 1,950,000, white cells 12,440, myeloblasts 34 %, neutrophile myelocytes 3 %, neutrophile metamyelocytes 11 %, neutrophile staff cells 4 %, segmented neutrophils 12 %, lymphocytes 35 %. Wassermann negative Sternal punctate: Myeloblasts 84 %, promyelocytes 2 %, neutrophile myelocytes 5 % Died 3½ months after admission. Necropsy (470/44) Spleen 775 g; leukemic infiltration in spleen, liver and kidney.—Diagnosis: *Chronic myelogenous leukemia.*

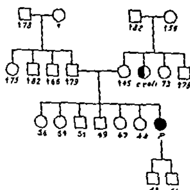
MOTHER'S BROTHER —Died, Jan 15th, 1938, aged 54, of cancer of the rectum (Frederiksberg Hospital; service A, no 50/38).

MOTHER'S MOTHER —Died, July 8th, 1902, aged 62, of cancer of the uterus (death certificate).



Pedigree 112

PROBAND (State Hospital; service B, no 936/42) —Foundry-workman. Formerly well When 42 admitted owing to extreme fatigue, increasing pallor and enlarging lymp nodes in axillae and groin The spleen palpable 4 cm below the costal margin. Hemoglobin 38 %, red cells 2,100,000, white cells 26,000, hemocytoblasts + myeloblasts 40 %, neutrophile myelocytes 24 %, neutrophile staff cells 10 %, segmented neutrophils 21 %, lymphocytes 3 %, thrombocytes 192,000 Wassermann negative Necropsy (372/42). Leukemic infiltration in liver, kidney, lymph nodes, pancreas and bone marrow —Diagnosis: *Chronic myelogenous leukemia*

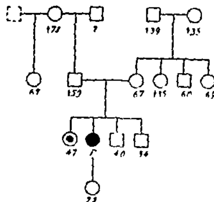


Pedigree 113

PROBAND (Bispebjerg Hospital, service B, no 192/4/45) —Provision dealer Two childbirths When 28 erythema nodosum When 41 admitted owing to increasing fatigue, pain below left costal margin and increasing circumference of the abdomen Examination showed walnut-sized lymph

nodes in the left axilla, the spleen extending to the midline and to 5 cm from the iliac crest; the liver not enlarged. Hemoglobin 36 %, red cells 2,290,000, white cells 118,000, myeloblasts 42 %, myelocytes 5 %, segmented neutrophils 49 %, lymphocytes 4 %; thrombocytes 187,000. Wassermann negative. Gradually there came infiltrations in the skin and melena, but the patient wished to be discharged. Still living, but has not been examined since.—Diagnosis: *Chronic myelogenous leukemia.*

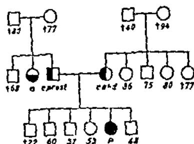
MOTHER'S SISTER.—*Died, March 26th, 1929, aged 69, of cancer of the colon (death certificate).*



Pedigree 114

PROBAND (State Hospital, service A, no 880/42).—Housewife. One childbirth, three abortions. Formerly well. When 41 fatigue, pallor and increase of circumference of abdomen. At admission the spleen extended 3 cm below the costal margin. Hemoglobin 48 %, red cells 2,750,000, white cells 305,000, promyelocytes 1 %, neutrophile myelocytes 24 %, eosinophile myelocytes 5 %, neutrophile metamyelocytes 10 %, neutrophile staff cells + segmented neutrophils 49 %, segmented eosinophils 4 %, basophils in all 2 %; thrombocytes 720,000. Wassermann negative. Temporarily good effect of roentgen treatment. Followed for 3 years. Still living.—Diagnosis: *Chronic myelogenous leukemia.*

SISTER.—Living, aged 47, has diffuse struma, exophthalmus, is thin in spite of great appetite, nervous and suffering from perspiration.—Diagnosis: Graves' disease.



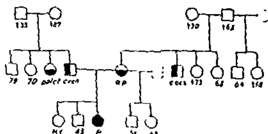
Pedigree 115.

PROBAND (County Hospital, Gentofte; service B, no 136/36)—Housewife Never pregnant When 2 scarlatina. When 40 admitted owing to fatigue, fever and loss of weight Examination showed necroses of mucous membranes, hazelnut-sized lymph nodes, no enlargement of the spleen Hemoglobin 28 %, red cells 1,930,000, white cells 230,000, myeloblasts 88½ %, myelocytes 1 % Wassermann negative Sternal punctate dominated by cells of the myeloid series. Duration of illness at least 6 months No necropsy—Diagnosis *Chronic myelogenous leukemia*

FATHER—Died, Nov 30th, 1930, aged 76, of cancer of the prostate (death certificate)

FATHER'S SISTER.—Died, May 12th, 1899, aged 49, of chronic anemia of several years duration (death certificate)

MOTHER—Died, Sep 18th, 1937, aged 72, of cancer of the abdomen (death certificate)



Pedigree 116

PROBAND (County Hospital, Gentofte, service C, no 810/40)—Housekeeper Never pregnant Seven times hospitalised for celitis, well since operated on when 28 (case record lost) When 40 admitted with arthralgias, fever and hemorrhagic diathesis The spleen extended to the midline. Hemoglobin 48 %, red cells 2,130,000, white cells 603,000, myeloblasts 20 %,

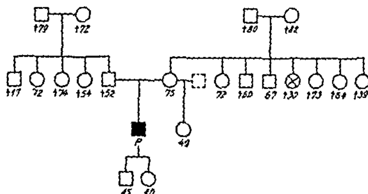
neutrophile myelocytes 36 %, neutrophile staff cells 19 %, segmented neutrophils 17 %, eosinophils 3 %, monocytes 1 %, lymphocytes 4 %, thrombocytes 164,000. Wassermann negative Effect of roentgen treatment slight. Followed for 9 months. Necropsy (127/40): Spleen 30 × 18 × 9 cm, liver 30 × 26 × 9 cm; leukemic infiltration in spleen and liver.—Diagnosis: *Chronic myelogenous leukemia.*

FATHER.—Died, Sep. 17th, 1936, aged 64, of metastasising tumor of the kidney (death certificate)

FATHER'S SISTER.—Living, aged 67, but suffers from polycytemia vera (Finsen Institute; med service, no. 6863). Was well until she, when 60, got headaches, heat flushes, nosebleeds and deep red color of face, hands and feet Hemoglobin 140 %, red cells 8,390,000, white cells 6,740. Sternal punctate: Very strong erythropoiesis; cell distribution otherwise normal Good effect of roentgen treatment

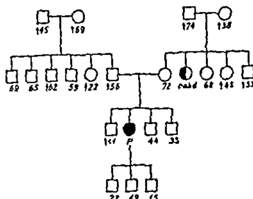
MOTHER—Living, aged 71. In the last two years treated with stomach preparations for anemia, having got sore tongue and paresthesias; but has repeatedly neglected to keep up the treatment, with the result that there each time developed anemia, glossitis and myelopathy Besides, she has diabetes mellitus in a mild degree.

MOTHER'S BROTHER—Died, Sep. 23rd, 1919, aged 53, of cancer of the esophagus (death certificate).



Pedigree 117.

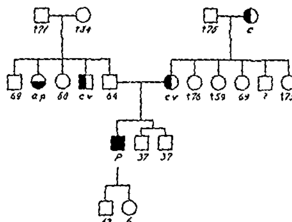
PROBAND (Municipal Hospital, service 2, no. 909/42)—Mechanic Formerly well. When 39 loss of weight, fatigue and increasing anemia The spleen extending about 8 cm, the liver 2 cm., below the costal margin Hemoglobin 83 %, red cells 3,500,000, white cells 100,000, myeloblasts 4 %, neutrophile myelocytes 3 %, neutrophile metamyelocytes 5 %, neutrophile staff cells 16 %, segmented neutrophils 60 %, eosinophils 1 %, erythroblasts 6 % Wassermann negative Temporarily good effect of roentgen treatment. Followed for about 6 months. Necropsy (452/42): Myeloid leukemic infiltration in liver, spleen and pleura—Diagnosis *Chronic myelogenous leukemia.*



Pedigree 118.

PROBAND (State Hospital; service A, no 888/45) —Housewife. Three childbirths. When 26 non-specific abdominal inflammation; for several years suffering from migraine When 39 admitted owing to fatigue, loss of weight and hemorrhagic diathesis. The spleen extending to the midline and 5 cm below the umbilicus Hemoglobin 63 %, red cells 2,950,000, white cells 80,000, myeloblasts 7 %, promyelocytes 6½ %, neutrophile myelocytes 19 %, eosinophile myelocytes 2½ %, neutrophile metamyelocytes 6½ %, neutrophile staff cells 12½ %, segmented neutrophils 42 %; thrombocytes 430,000 Wassermann negative Sternal punctate Myeloblasts 28 % Good effect of roentgen treatment. Hospitalised five times in the course of 2 years Still living —Diagnosis *Chronic myelogenous leukemia*

MOTHER'S SISTER.—Died, Feb 13th, 1939, aged 70, of cancer of the abdomen (death certificate)



Pedigree 119

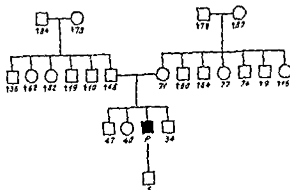
PROBAND (Sundby Hospital; service M, no 739/45)—Merchant. Since 18 paroxysmal tachycardia, when 33 pleurisy When 38 admitted owing to increasing loss of weight and nervosity. Examination showed Traube's space diminished, no enlarged lymph nodes. Hemoglobin 69 %, red cells 3,500,000, white cells 137,600, myeloblasts 4 %, promyelocytes 6 %, neutrophile myelocytes 12 %, neutrophile metamyelocytes 29 %, segmented neutrophils 39 %, eosinophils 2 %, lymphocytes 8 % Sternal punctate· Chiefly myelocytes, sparse erythropoiesis Wassermann negative Temporarily good effect of roentgen treatment Followed for 1 year. Still living—Diagnosis· *Chronic myelogenous leukemia.*

FATHER'S SISTER—Died, Dec 28th, 1921, aged 48, of pernicious anemia, verified by death certificate. Had for a couple of years been very tired and anemic, with smarting in tongue and paresthesias in fingers and toes, some dyspepsia and occasional nosebleeds

FATHER'S BROTHER—Died, Feb 2nd, 1937, aged 52, of cancer of the stomach (death certificate)

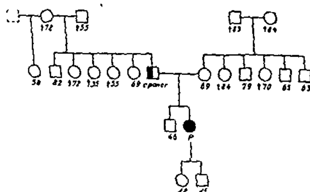
MOTHER—Died, Sep 23rd, 1918, aged 45, of cancer of the stomach (death certificate).

MOTHER'S MOTHER—Died, April 26th, 1880, aged 41, according to the statements of several relatives, of cancer



Pedigree 120

PROBAND (County Hospital, Gentofte: service C, no 1428/43).—Shop-assistant. When 36 "influenza", and shortly afterwards admitted owing to loss of weight and night-sweats Examination showed enlarged lymph nodes, up to hazelnut-size, in the groin, and the spleen extending to the umbilicus. Hemoglobin 66 %, red cells 3,320,000, white cells 308,800, myeloblasts 4 %, myelocytes 23 %, neutrophile staff cells 39 %, segmented neutrophils 30 %, eosinophils 1 %, basophils 1 %, lymphocytes 2 % Wassermann negative Good effect of roentgen treatment. Admitted 10 times At last admission: Hemoglobin 63 %, white cells 494,200 Necropsy (368/43) Spleen 30 × 18 × 10 cm, liver 29 × 27 × 10 cm—Diagnosis Chronic myelogenous leukemia

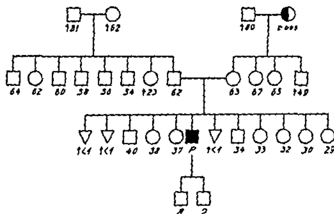


Pedigree 121

PROBAND (Bispebjerg Hospital, service B, no 34/1/38) —Housewife Two childbirths Formerly well. When 34 admitted because she had noticed

a swelling in her abdomen No enlargement of lymph nodes, but the spleen extended to the midline. Hemoglobin 52 %, red cells 3,210,000, white cells 183,000, myeloblasts 3 %, promyelocytes 19 %, neutrophile myelocytes 20 %, neutrophile metamyelocytes 9 %, neutrophile staff cells 15 %, segmented neutrophils 19 %, eosinophils 6 %, basophils 3 %, lymphocytes 6 %. Wassermann negative. Temporarily good effect of roentgen treatment Followed for 3 years. Died suddenly of pulmonary embolus Necropsy: Leukemic infiltration in lymph nodes, liver and kidney.—Diagnosis: *Chronic myelogenous leukemia*

FATHER.—Died, May 3rd, 1937, aged 55, of cancer of the pancreas (death certificate).

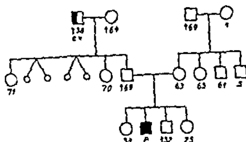


Pedigree 122

PROBAND (Radium Center, no 37754)—Workingman Formerly well When 34 admitted owing to priapism The spleen extended 5 cm, the liver 3 cm below the costal margin. Hemoglobin 47 %, red cells 2,480,000, white cells 244,800, myeloblasts 7 %, promyelocytes 6½ %, neutrophile myelocytes 13½ %, neutrophile metamyelocytes 16½ %, neutrophile staff cells 25 %, segmented neutrophils 34 %; thrombocytes 280,000 Sternal punctate Myeloblasts 3 %, promyelocytes 12.7 %, neutrophile myelocytes 24 2 %, basophils 3.4 % Wassermann negative Following roentgen treatment, the white cell count was 20,880 Patient still living—Diagnosis, *Chronic myelogenous leukemia*

MOTHER'S MOTHER—Died, July 28th, 1911, aged 63, during a hematemesis, after having suffered for a year from increasing difficulty of deglutition, regurgitations and emaciation—Diagnosis Cancer of the esophagus

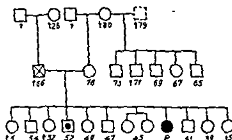
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Pedigree 123.

PROBAND (St Joseph's Hospital, no. 423/44) —Dentist Well until he, when 34, got hemorrhagic diathesis and a feeling of heaviness below the left costal margin No enlargement of lymph nodes, the spleen not palpable. Hemoglobin 70 %, red cells 3,800,000, white cells 132,000, myeloblasts 7 %, neutrophile myelocytes 8 %, neutrophile metamyelocytes 9 %, lymphocytes 17 %, segmented neutrophils 54 %, eosinophils 5 %; thrombocytes 114,000 Wassermann negative The myeloblast percentage increasing Duration of illness at least 1 year No necropsy —Diagnosis: *Chronic myelogerous leukemia*

FATHER'S FATHER.—Died, 1882, aged 38, according to statements of relatives, of cancer of the stomach

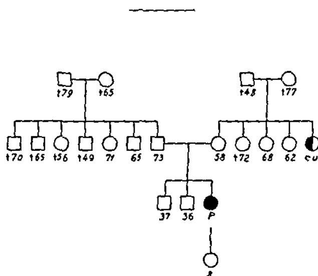


Pedigree 124

PROBAND (Sundby Hospital, service M, no 1512/42) —Housewife Never pregnant Repeated operations for benign ovarian tumor. When 33 suddenly ill with pressing pains below left costal margin. Examination showed the spleen extending to the midline and 3 cm below the umbilicus Hemoglobin 57 %, red cells 3,270,000, white cells 220,000, myeloblasts 2 %, promyelocytes 3 %, neutrophile myelocytes 20 %, neutrophile metamyelocytes 15 %, neutrophile staff cells + segmented neutrophils 57 % Good effect of roentgen treatment A year later re-admitted with large tumor of the spleen and

white cell count 137,000, 37 % of which were myeloblasts Wassermann negative. Observed for 1 year. No necropsy.—Diagnosis: *Chronic myelogenous leukemia*

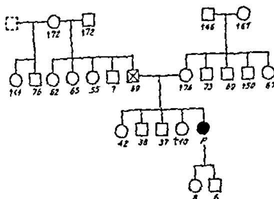
BROTHER.—Living, aged 52. When 51 thyroidectomy after the basal metabolic rate by treatment with diiodotyrosine had been reduced from 160 to 130 %.—Diagnosis: Graves' disease (State Hospital; service C, no 855/44)



Pedigree 125

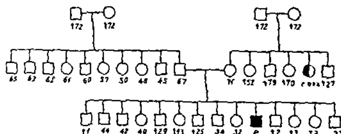
PROBAND (State Hospital; service A, no. 952/45).—Housewife One childbirth Well until, when 51, admitted owing to fatigue, fever and hemorrhagic diathesis Moderate, universal enlargement of the lymph nodes, spleen extending 3 cm to the right of the umbilicus and to the symphysis Hemoglobin 50 %, red cells 2,800,000, white cells 602,000, myeloblasts 4 %, promyelocytes 8 %, neutrophile myelocytes 45 %, neutrophile metamyelocytes 1/2 %, neutrophile staff cells 11 %, segmented neutrophils 17 1/2 %, eosinophils 3 %, thrombocytes 180,000 Wassermann negative Still living.—Diagnosis. *Chronic myelogenous leukemia*

MOTHER'S SISTER.—Died, March 21st, 1926, aged 47, of cancer of the uterus (death certificate)



Pedigree 126

PROBAND (Bispebjerg Hospital, service B, no 90/4/44) —Housewife Two childbirths When 31 admitted for "influenza" Examination showed moderate enlargement of the lymph nodes, the spleen extending to the right of and below the umbilicus Hemoglobin 52 %, red cells 3,270,000, white cells 327,200, myeloblasts 6 %, promyelocytes 12 %, myelocytes 13 %, neutrophile staff cells 15 %, segmented neutrophile 10 %, eosinophils 10 %, basophils 6 % Wassermann negative After roentgen treatment there was a slight fall in the white cell count and diminution in the enlargement of the spleen Followed for 2 years Necropsy· Spleen 2850 g, liver 2050 g— Diagnosis Chronic *myelogenous leukemia*

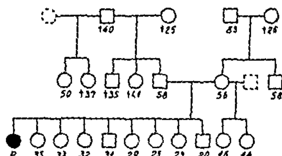


Pedigree 127

PROBAND (County Hospital, Gentofte, service B, no 829/45) —Workingman When 27 concussion of the brain and fracture of the clavicle When 30 sticking pains below *left* costal margin, fatigue, night-sweats and loss of weight Hemoglobin 45 %, white cells 310 000, myeloblasts 5 %, promyelocytes 4 %, myelocytes 29 %, metamyelocytes 21 % staff cells 17 %,

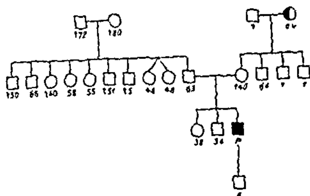
segmented neutrophils 20 %, lymphocytes 4 %. Sternal punctate: Myeloblasts 6 %, promyelocytes 24 %, neutrophile metamyelocytes + neutrophile staff cells 32 %, segmented neutrophils 27 %, lymphocytes 2 %, scant erythropoiesis. Wassermann negative. Temporarily good effect of roentgen treatment Still living.—Diagnosis: *Chronic myelogenous leukemia*

MOTHER'S SISTER.—Died, Nov 13th, 1933, aged 70, of cancer of the esophagus (death certificate).



Pedigree 128

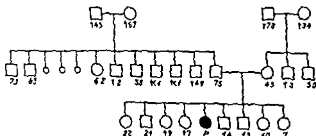
PROBAND (Bispebjerg Hospital, service C, no 30/5/42)—Housemaid Never pregnant. When 31 admitted in order to be treated for blood disease Hemoglobin 84 %, red cells 3,760,000, white cells 17,120, myeloblasts 1 %, myelocytes 3 %, neutrophils 88 %, eosinophils 1 %, monocytes 3 %. Sternal punctate, hyperplastic, myeloid cells dominant, with shift to the left Wassermann negative Gradually there came considerable enlargement of the spleen Temporarily good effect of roentgen treatment Followed for about 4 years No necropsy—Diagnosis: *Chronic myelogenous leukemia*



Pedigree 129.

PROBAND (Municipal Hospital; service 3, no 1214/43) —Tramway employee Formerly well. When 28 admitted owing to fatigue, loss of weight and increasing pallor Hemoglobin 62 %, white cells 160,000, neutrophile myelocytes 39 %, neutrophile metamyelocytes 47 %, neutrophile staff cells 11 %, lymphocytes 3 %. A year later the spleen extended to the midline and the iliac crest, and there was hemorrhagic diathesis Wassermann negative Followed for 1 year No necropsy —Diagnosis *Chronic myelogenous leukemia*

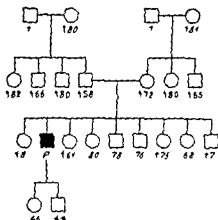
MOTHER'S MOTHER.—Died, Dec. 16th, 1912, aged 50, of cancer of the stomach (death certificate)



Pedigree 130

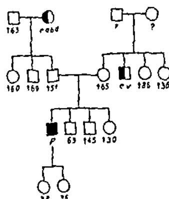
PROBAND (Sundby Hospital, service M, no 1731/42) —Daughter of dock-laborer From her 4th to her 10th year treated for pulmonary tuberculosis and misery When 12 admitted owing to increasing fatigue and loss of weight Examination showed the tonsils large, the spleen lightly enlarged. Hemoglobin 63 %, red cells 3 020,000, white cells 3,200, mononuclears 79 %,

Wassermann negative Mantoux positive. Roentgen examination of lungs: No infiltrates, but hili large. The sternal punctate dominated by promyelocytes and myelocytes, besides, a number of myelocytes, the erythropoiesis somewhat diminished Four months later: Hemoglobin 43 %, falling to 27 %; white cells 24,100. Followed for 18 months. Necropsy: Spleen 16 × 7½ × 5½ cm, lymph nodes in hilus of the lung and in the mesentery large — Diagnosis. *Chronic myelogenous leukemia*



Pedigree 131

PROBAND (Frederiksberg Hospital; service B, no 233/36) —Manufacturer When 15 appendectomy, otherwise well until he, when 74, was admitted suffering from fever and hemorrhagic diathesis. The spleen not palpable Hemoglobin 67 %, red cells 3,380,000, white cells 82,000, lymphocytes 74 %, lymphoblasts 23 %, thrombocytes 37,000 Wassermann negative. Died under a copious hemoptysis No necropsy —Diagnosis *Acute lymphogenous leukemia*



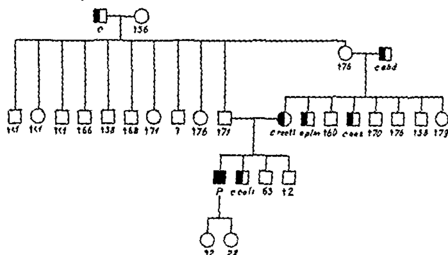
Pedigree 132

PROBAND (Municipal Hospital, service 3, no 1966a/44) —Office-manager Well until his 50th year of age, when a urethral calculus passed When 67 admitted with the *diagnosis Cholecystitis No enlargement of lymph nodes,* spleen or liver Hemoglobin 41 %, red cells 1,900,000, white cells 14,200, large lymphocytes 5 %, small lymphocytes 59 %, monocytes 3 %, plasma cells 1 %, neutrophile staff cells 6 %, segmented neutrophils 25 %, a few *erythroblasts Thrombocytes* 45,500 *Wassermann negative Sternal punctate*· Lymphocytes 77 %. After a while the spleen could be palpated The patient wished to be discharged and died in his home after at least 3 months' illness —Diagnosis *Acute lymphogenous leukemia*

FATHER S MOTHER —Died, Sep 1901, aged 62, of ileus, after 6 months' increasing fatigue and emaciation —Diagnosis Cancer of the abdomen.

MOTHER S BROTHER —Died, Apr 19th, 1907, aged 74, of cancer of the stomach (death certificate)

Pedigree 133



Pedigree 133

PROBAND (County Hospital, Gentofte; service B, no. 421/37).—Architect. Well until he, when 63, was admitted after having suffered for a couple of years from dyspnea, increasing fatigue and edema of the ankles Examination showed slight, universal enlargement of the lymph nodes, and the spleen extending to the left iliac fossa and almost to the midline, the liver palpable 3 cm below the costal margin Hemoglobin 54 %, red cells 2,600,000, white cells 40,200, lymphoblasts 30 %, lymphocytes 68 % Wassermann negative. Gradually marked hemorrhagic diathesis developed, and the patient died 1 month after admission No necropsy—Diagnosis. *Acute lymphogenous leukemia*

BROTHER.—*Died, Jan 20th, 1941*, aged 65, of cardiac disease, but had a few years before been operated on (colostomy) for a tumor of the large intestine—Diagnosis Cancer of the colon.

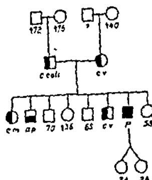
MOTHER—Died, Apr 21st, 1910, aged 64, of cancer of the rectum (death certificate)

MOTHER'S BROTHER—Died, May 6th, 1907, aged 65, of cancer of the right lung (death certificate)

MOTHER S BROTHER—Died, Nov 29th, 1927, aged 71, of cancer of the esophagus (death certificate)

MOTHER'S FATHER—Died, Nov 24th, 1860, aged 52, of cancer of the abdomen (death certificate)

FATHER'S FATHER—Died, May 30th, 1855, aged 64, of cancer (death certificate).



Pedigree 134

PROBAND (Frederiksberg Hospital, service E, no 2556/44).—Milk-controller When 42 pneumonia, when 53 nephrolithotomy, when 54 herniotomy From his 59th year diabetes mellitus, but no insulin treatment When 59 admitted owing to fever. Examination showed a few hazelnut-sized lymph nodes in the axillae, and the spleen extending 8 cm below the costal margin Hemoglobin 55 %, red cells 1,870,000, white cells 65,000, lymphoblasts 28 %, large lymphocytes 11 %, small lymphocytes 22 %, Wassermann negative Sternal punctate. Lymphoid cells 81 % The blood sugar increasing Got insulin, but died 1 month after admission Necropsy (389/44): Spleen 21 × 13 × 6 cm, liver 30 × 18 × 8 cm, leukemic infiltration in liver, spleen and bone marrow.—Diagnosis *Acute lymphogenous leukemia*

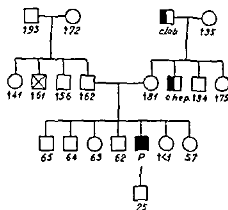
SISTER.—Died, Aug 15th, 1917, aged 45, of *breast cancer* (death certificate)

BROTHER.—Living, aged 72, suffering from pernicious anemia diagnosed 13 years ago (Frederiksberg Hospital, service B, no 928/32) Glossitis, gastric achylia, hemoglobin 60 %, red cells 1,760,000, white cells 2,520, *neutrophils* 73 %, many megalocytes, after specific treatment typical reticulocyte response

BROTHER.—*Died*, Jan 12th, 1940, aged 57, of cancer of the stomach (death certificate)

FATHER.—Died, Oct. 10th, 1918, aged 70, of cancer of the sigmoid (death certificate)

MOTHER.—Died, Dec 14th, 1927, aged 80, of cancer of the stomach (death certificate)



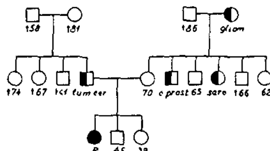
Pedigree 135

PROBAND (Sundby Hospital, service M, no 454/44)—Civil engineer. When 49 herniotomy, when 58 "influenza" twice, after which time he was subfebrile, with increasing fatigue, cough and expectoration. Examination showed considerable universal enlargement of the lymph nodes, the liver palpable 5 cm. below the costal margin, the spleen extending almost to the umbilicus Hemoglobin 70 %, red cells 3,490,000, white cells 251,600, large lymphocytes 70 %, small lymphocytes 27 %. Wassermann negative Roentgen treatment of doubtful effect Died 3 weeks after admission Necropsy (65/44) Spleen 1450 g; leukemic infiltration in lymph nodes, spleen, liver and bone marrow—Diagnosis: *Acute lymphogenous leukemia*

MOTHER'S BROTHER—Died, Jan 10th, 1924, aged 74, of cancer of the liver (death certificate)

MOTHER'S FATHER—Died, Nov 16th, 1888, aged 69 Had a chronic, growing ulcer on the lower lip.—Diagnosis Cancer of the lip

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Pedigree 136

PROBAND (Frederiksberg Hospital, service E, no 408/41)—Housewife Never pregnant When 42 "angina", a month later admitted owing to persistent fever and dyspnea No enlargement of lymph nodes, but after a

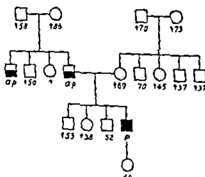
while the liver extended 3 cm, the spleen 8 cm, below the costal margin Hemoglobin 49 %, white cells 2,280, large lymphocytes 34 %, small lymphocytes 50 %, monocytes 12 %, thrombocytes 186,000 Sternal punctate: Lymphoblasts 56 %, lymphocytes 17 %, erythroblasts 17 %. Followed for 5 months Necropsy (100/41)· Leukemic infiltration in spleen, liver, kidney and tonsils —Diagnosis *Acute lymphogenous leukemia*

FATHER —Died, Oct 20th, 1930, aged 63, of cerebral tumor (Frederiksberg Hospital, service D, no 560/30).

MOTHER'S BROTHER —Died, Apr 15th, 1940, aged 67, of cancer of the prostate (death certificate)

MOTHER'S SISTER —Died, July 23rd, 1941, aged 65, of melanosarcoma of the eye (death certificate).

MOTHER'S SISTER.—Died, Dec 6th, 1908, aged 62, of cerebral glioma (death certificate)



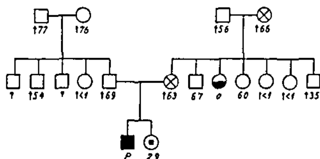
Pedigree 137

PROBAND (County Hospital, Gentofte, service B, no 1220/39).—Chief-assistant For several years suffering from cardiac neurosis, when 41 four times angina and peritonsillar abscess Since then constantly enlarged lymph nodes in the neck, after a while also in the axillae and groin, besides skin eruptions The spleen extending to the umbilicus, the liver palpable 2 cm below the costal margin Hemoglobin 47 %, red cells 1,820,000, white cells 144 800, lymphoblasts 60 %, lymphocytes 35 % Wassermann negative. Shortly before death the hemoglobin fell rapidly to 10 % Necropsy, Spleen 21 × 12 × 6 cm, leukemic infiltration in liver, kidney and bone marrow — Diagnosis *Acute lymphogenous leukemia*

FATHER —Died, June 11th, 1941, aged 75, of pernicious anemia (death certificate) He had for many years got along thanks to specific treatment,

but despite this myelopathies developed and the anemia became more severe

FATHER'S BROTHER.—Died, March 21st, 1925, of pernicious anemia (death certificate).



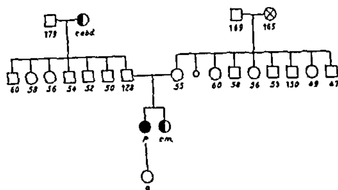
Pedigree 138.

PROBAND (Municipal Hospital; service 2, no. *139/8/41)*—*Commercial* agent Wen 31 admitted with maxillary ostitis and phlegmon of the palate, but as his hemoglobin rate was 65 % he was transferred to the medical service The liver was palpable just below the costal margin, the spleen not enlarged Hemoglobin 56 %, red cells 2,100,000, white cells 152,000, small lymphocytes 61 %, large lymphocytes 21 % Wassermann negative Died 2 weeks after admission Necropsy (467/41) Leukemic infiltration in kidney and liver—Diagnosis· *Acute lymphogenous leukemia*

SISTER—Living, aged 29 When about 24 she had a typical myxedema, but is now getting along well on thyroid medications

MOTHER'S SISTER—Living, aged 62 Has for many years suffered from simple anemia, but gets along on iron medications When she neglects these, the anemia recurs Besides, she suffers from gastric achylia

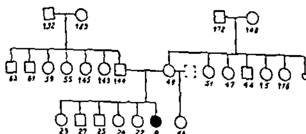
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Pedigree 139

PROBAND (Sundby Hospital, service M, no 1492/43)—Housewife One childbirth When 9 recurrent rheumatic fever complicated by cardiac disorder When 27, after a dental abscess, very fatigued, suffering from vertigo, increasing pallor, slight, diffuse enlargement of the lymph nodes No enlargement of spleen or liver Hemoglobin 28 %, red cells 1,350,000, white cells 5,400, lymphocytes 84 %, thrombocytes 28,000, Wassermann [illegible] 11 × 8 × 4 cm, [illegible] nous leukemia [illegible] cancer (Sundby Hospital, surgical service, no 2113/41)

FATHER'S MOTHER—Died, Apr 28th, 1943, aged 79, of cancer of the abdomen (death certificate)

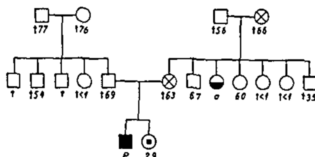


Pedigree 140

PROBAND (Radium Center, no 39223)—Warehouse assistant Never pregnant When 12 appendectomy, when 20 tonsillectomy on account of recurrent tonsillitis When 21 *admitted* owing to hemorrhagic diathesis and

but despite this myelopathies developed and the anemia became more severe

FATHER'S BROTHER.—Died, March 21st, 1925, of pernicious anemia (death certificate).



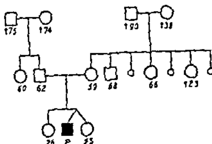
Pedigree 138.

PROBAND (Municipal Hospital; service 2, no 139/8/41).—Commercial agent. Wen 31 admitted with maxillary ostitis and phlegmon of the palate, but as his hemoglobin rate was 65 % he was transferred to the medical service. The liver was palpable just below the costal margin, the spleen not enlarged. Hemoglobin 56 %, red cells 2,100,000, white cells 152,000, small lymphocytes 61 %, large lymphocytes 21 % Wassermann negative Died 2 weeks after admission. Necropsy (467/41): Leukemic infiltration in kidney and liver.—Diagnosis. *Acute lymphogenous leukemia*

SISTER.—Living, aged 29 When about 24 she had a typical myxedema, but is now getting along well on thyroid medications

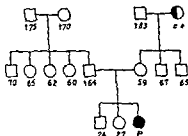
MOTHER'S SISTER.—Living, aged 62 Has for many years suffered from simple anemia, but gets along on iron medications When she neglects these, the anemia recurs Besides, she suffers from gastric achylia

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Pedigree 142

PROBAND (Municipal Hospital, service 2, no. 428/42)—Turner. When 19 admitted owing to increasing fatigue, headaches and some attacks of syncope Examination showed necrotising stomatitis, some enlargement of lymph nodes and liver extending 1 cm. below the costal margin. *No enlargement* of the spleen Hemoglobin 49 %, red cells 1,960,000, white cells 40 000, increasing to 62,000, large lymphocytes 92 %, *small lymphocytes* 2 %, neutrophils 2 %, erythroblasts 4 % Thrombocytes 215,000 Wassermann negative, Bunnell's test negative Died 11 days after admission Necropsy (212/42): Marked enlargement of spleen and liver, the bone *marrow* greyish, hyperplastic—Diagnosis *Acute lymphogenous leukemia*



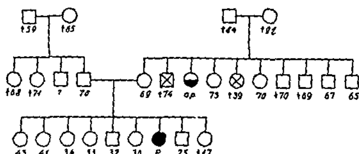
Pedigree 143

PROBAND (State Hospital, service B, *no* 332/38)—Domestic-science pupil Formerly well When 18 admitted owing to extreme fatigue Examination showed a few pea-sized lymph nodes in neck, axillae and groin No enlargement of the spleen Hemoglobin 29 %, white cells 34,500, promyelocytes 0 7 %, myelocytes 1.3 %, neutrophile metamyelocytes 2 %, neutrophile staff cells 1 3 %, segmented neutrophils 1 7 %, eosinophils 1 6 %, monocytes 0 7 % lymphoblasts 84 7 % (oxydase-negative), lymphocytes 6 % Wassermann negative Roentgen treatment without effect 3 months after appearance of the first symptoms Necropsy (129/38). Spleen 920 g, liver 1 520 g, with many infiltrates—*Diagnosis* *Acute lymphogenous leukemia*

MOTHER'S MOTHER.—*Died*, 1895, aged 72 Had a chronic, steadily growing ulcer in one temple—Diagnosis Cancer of the skin

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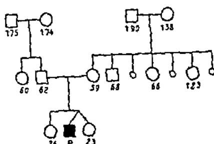
moderate, universal enlargement of the lymph nodes. Hemoglobin 29 %, red cells 1,200,000, white cell count increasing to 120,000, 98½ % of which were lymphoblasts and lymphocytes Thrombocytes 23,000. Wassermann negative No necropsy.—Diagnosis· *Acute lymphogenous leukemia.*



Pedigree 141

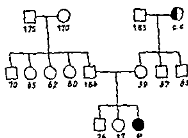
PROBAND (Frederiksberg Hospital, service A, no 1764/38)—Shop assistant Never pregnant. When 21 admitted owing to sudden attacks of abdominal colic Examination showed moderate enlargement of all palpable lymph nodes, the spleen and liver extending 2 cm below the costal margin Hemoglobin 86 %, red cells 4,280,000, white cells 62,200, large lymphocytes 71 %, small lymphocytes 5 %, lymphoblasts 2 %, neutrophils 22 % Wassermann negative. Gradually hemorrhagic diathesis developed, and 5 days after admission she died Necropsy (303/38) Leukemic infiltration in lymph nodes, stomach and myocardium—Diagnosis *Acute lymphogenous leukemia*

MOTHER'S SISTER—Died, Apr 29th, 1928, aged 66, of pernicious anemia (death certificate) *She had been anemic for many years, sometimes with* hemoglobin rate of 30 %. Iron therapy had proved ineffective, but arsenic had done some good In 1927 her hemoglobin rate was 27 %, and after treatment with raw liver it rose to 54 %



Pedigree 142

PROBAND (Municipal Hospital, service 2, no 428/42)—Turner When 19 admitted owing to increasing fatigue, headaches and some attacks of syncope Examination showed necrotising stomatitis, some enlargement of lymph nodes and liver extending 1 cm. below the costal margin No enlargement of the spleen Hemoglobin 49 %, red cells 1,960,000, white cells 40,000, increasing to 62,000, large lymphocytes 92 %, small lymphocytes 2 %, neutrophils 2 %, erythroblasts 4 % Thrombocytes 215,000 Wassermann negative, Bunnell's test negative Died 11 days after admission Necropsy (212/42) Marked enlargement of spleen and liver; the bone marrow greyish, hyperplastic—Diagnosis *Acute lymphogenous leukemia*

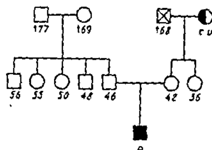


Pedigree 143

PROBAND (State Hospital, service B, no 332/38)—Domestic-science pupil Formerly well When 18 admitted owing to extreme fatigue Examination showed a few pea-sized lymph nodes in neck, axillae and groin No enlargement of the spleen Hemoglobin 29 %, white cells 34,500, promyelocytes 0 7 %, myelocytes 1.3 %, neutrophile metamyelocytes 2 %, neutrophile staff cells 1 3 %, segmented neutrophils 1 7 %, eosinophils 1 6 %, monocytes 0 7 %, lymphoblasts 84 7 % (oxydase-negative), lymphocytes 6 % Wassermann negative Roentgen treatment without effect. 3 months after appearance of the first symptoms Necropsy (129/38) Spleen 920 g., liver 1 520 g with many infiltrates—Diagnosis *Acute lymphogenous leukemia*

MOTHER'S MOTHER—Died, 1895, aged 72 Had a chronic, steadily growing ulcer in one temple—Diagnosis Cancer of the skin

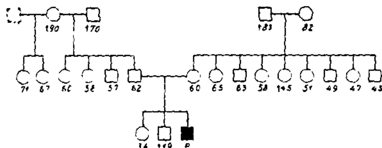
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Pedigree 144.

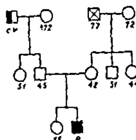
PROBAND (Municipal Hospital, service 7, no. 738/42) —Apprentice When 1 year old pneumonia, when 18 *increasing fatigue, loss of weight, pain in* the lower jaw, considerable, universal enlargement of the lymph nodes, the spleen palpable 8 cm below the costal margin Hemoglobin 54 %, red cells 3,000,000, white cells 77,000, small lymphocytes 8½ %, immature lymphocytes 89½ %, segmented neutrophils 3½ % Thrombocytes 198,000. Bunnel's test atypical. Wassermann negative Temporarily good effect of roentgen treatment, but the differential count unchanged Died at home shortly afterwards —Diagnosis *Acute lymphogenous leukemia*

MOTHER'S MOTHER.—Died, Aug. 27th, 1943, aged 62, of uterine cancer (Radium Center, Copenhagen, no. 27307).



Pedigree 145

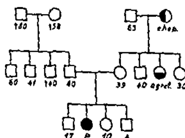
PROBAND (Blegdam Hospital, no 49/36) —Son of cigarmaker Had had the usual children's diseases When 10 admitted owing to fatigue and hemorrhagic diathesis The lymph nodes in the neck bean-sized, spleen and liver not enlarged Hemoglobin 42 %, red cells 2,340,000, white cells 272,000, lymphoblasts 74 %, lymphocytes 25 % Observed for 4 weeks Terminally White cells 836,000, 10 % of which were typical small lymphocytes No necropsy —Diagnosis *Acute lymphogenous leukemia*



Pedigree 146

PROBAND (State Hospital, service G. no 702/45)—Son of assistant traffic manager Born 3 weeks before term When 5 parotitis From his 6th year marked lassitude and night-sweats After a slight trauma intense pain in thorax and abdomen Roentgen examination showed considerable diffuse halisteresis After hypercalcemia had been demonstrated, parathyreidectomy was performed, following which he was highly anemic and was hospitalised Examination after admission showed moderate enlargement of the lymph nodes and the spleen and liver extending 2 cm below the costal margin Hemoglobin 77 %, red cells 3,310,000, white cells 3,760, neutrophile staff cells 29 %, lymphocytes 70 %, thrombocytes 62,000 Moro negative Wassermann negative Died 17 days after admission Necropsy (349/45): Leukemic infiltration in kidney, liver, spleen and bone marrow.—Diagnosis: *Acute lymphogenous leukemia*

FATHER'S FATHER—Died, July 16th, 1920, aged 51, of cancer of the stomach (death certificate)

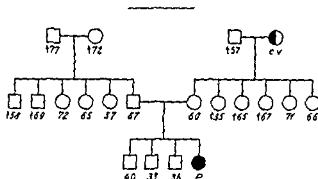


Pedigree 147.

PROBAND (Bispebjerg Hospital; service B. no 83/1/39)—Daughter of butcher Well until she, when 6, was admitted with high fever, abdominal pains and hemorrhagic diathesis Pea-sized lymph nodes in the neck, the spleen extending to 4 cm from the midline and the umbilicus Hemoglobin 35 % red cells 1,600 000, white cells 37,600, lymphoblasts 92 %, lymphocytes 6 %, thrombocytes 39,000 Wassermann negative Observed for 3 months White cell count towards the end 67,200 No necropsy—Diagnosis. *Acute lymphogenous leukemia*

MOTHER'S SISTER —Died, Nov. 6th, 1937, aged 28, of agranulocytosis (Blegdam Hospital, Copenhagen; no. 3215) Had been admitted suffering from high fever, gingivitis and epistaxis. Hemoglobin 73 %, red cells 3,550,000, white cells 419, falling to 206, lymphocytes 94 %, monocytes 4 %, segmented neutrophils 2 % The hemoglobin rate remained unchanged. Died 1 week after admission.

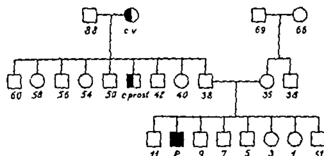
MOTHER'S MOTHER.—Died, Apr. 19th, 1928, aged 43, of cancer of the liver (death certificate).



Pedigree 148

PROBAND (Children's Hospital, Fuglebakken, no 177/37).—Daughter of tailor's cutter Born at term When 3 whooping-cough When 4½ languid, peevish, increasingly anemic and eventually hyperpyretic Examination showed universal enlargement of lymph nodes, the spleen extending 10 cm the liver 2 cm, below the costal margin Hemoglobin 11 %, red cells 930,000, white cells 6,000, lymphoblasts 11 %, large lymphocytes 11 %, small lymphocytes 78 % Wassermann negative The parents wished her discharged, and she died shortly afterwards at home —Diagnosis *Acute lymphogenous leukemia.*

MOTHER'S MOTHER —Died, Aug 29th, 1933, aged 86, of cancer of the stomach (death certificate)



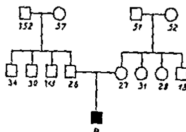
Pedigree 149

PROBAND (Frederiksberg Hospital, service C, no 314/40) —Son of nurseryman *Well until he, when 4 years old, after a "cold" became pale*

and constantly feverish, wherefore he was admitted No enlargement of the spleen Hemoglobin 36 %, white cells 3,900, large lymphocytes 14½ %, small lymphocytes 35½ %, a single normoblasts Sternal punctate: Lymphoblasts 77 %, lymphocytes 4 %. Wassermann negative. Repeated bloos smears showed increasing lymphocyte rate White cell count maximal 6,650 Died at home after 3 months' illness —Diagnosis· *Acute lymphogenous leukemia*

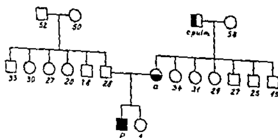
FATHER'S BROTHER.—Living, aged 46, has cancer of the prostate (County Hospital, Gentofte; roentgenol service, discharged Aug 9th, 1944).

FATHER'S MOTHER.—Died, Feb 23rd, 1921, aged 58, of cancer of the stomach (death certificate)



Pedigree 150

PROBAND (State Hospital, service G, no 886/45)—Son of slaughterhouse workman Born at term When 3 years old whooping cough, and 6 months later admitted owing to marked fatigue and pallor Lymph nodes moderately enlarged, liver extending 4 cm below the costal margin Hemoglobin 18 %, red cells 950,000, white cells 2,820, lymphocytes 87 %, Thrombocytes 13,000 Sternal punctate Lymphocytes 93⅓ % Died about 6 weeks after admission. Necropsy (457/45) Leukemic infiltration in liver, kidney, spleen and lymph nodes —Diagnosis *Acute lymphogenous leukemia*



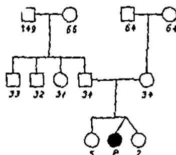
Pedigree 151

PROBAND (Frederiksberg Hospital, service B, no 191/43)—Son of bicycle dealer As infant pneumonia, when 18 months varicella. When 2½ years admitted with "angina" and fever Slight universal enlargement of

the lymph nodes, the liver palpable 1 cm. below the costal margin. Hemoglobin 51 %, red cells 3,770,000, white cells 2,200, lymphocytes 88 %, monocytes 3 %, neutrophils 9 %, thrombocytes 148,000. Wassermann negative. Tibial punctate: Large lymphocytes 0.4 %, small lymphocytes 88.4 %, erythroblasts 2.2 %. Observed for 2 months, during which time the white cell count rose to 13,700, still with 90 % of lymphocytes. No necropsy.—Diagnosis: *Acute lymphogenous leukemia.*

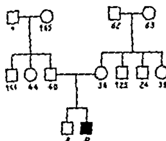
MOTHER.—Living, aged 25, suffering from monocytic anemia. According to communication from her physician her hemoglobin rate is about 70 %, in spite of iron therapy.

MOTHER'S FATHER.—Died, Nov. 22nd, 1944, aged 63, of cancer of the lung (death certificate)



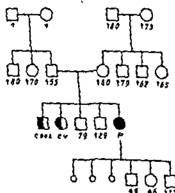
Pedigree 152.

PROBAND (Children's Hospital, Fuglebakken, no 837/43)—Daughter of workingman. Born at term, weighing 2700 g. When 1 year old whooping-cough. When nearly 2 admitted owing to hemorrhagic diathesis, loss of weight and fever. Hazelnut-sized lymph nodes in all regions, the liver palpable 4 cm. below the costal margin, the spleen extending to the umbilicus. Hemoglobin 34 %, red cells 1,520,000, white cells 12,800, lymphoblasts 68 %, lymphocytes 31 %. Died 5 years after admission. Necropsy: Leukemic infiltration in spleen and liver; spleen 6 × 8 × 15 cm., liver 5 × 11 × 19 cm.—Diagnosis: *Acute lymphogenous leukemia*



Pedigree 153

PROBAND (Queen Louise's Children's Hospital, no. 944/44)—Son of textile worker Born at term When 1 year old whooping-cough; 3 months later getting somnolent, peevish and sensitive to cold Admitted owing to hemorrhagic diathesis and increasing pallor Examination showed numerous suggillations, the tonsils hyperplastic, the lymph nodes moderately enlarged, the liver extending 2 cm., the spleen 8 cm, below the costal margin Hemoglobin 48 %, red cells 2,160,000, white cells 7,080, small lymphocytes 76 %, large lymphocytes 16 %, staff cells 1 %, segmented neutrophils $1^1/_2$ %, eosinophils 3 %, erythroblasts $^1/_2$ % Thrombocytes 9,800 Tibial punctate Stem cells 6 %, lymphoblasts 32 %, lymphocytes 62 %, a few promyelocytes Spleen and liver increased in size The hemoglobin rate decreased Wassermann negative Died after at least 6 months' illness Necropsy: Liver 940 g, spleen 290 g, marked leukemic infiltration in liver, spleen, kidney, bone marrow and lymph nodes—Diagnosis *Acute lymphogenous leukemia*



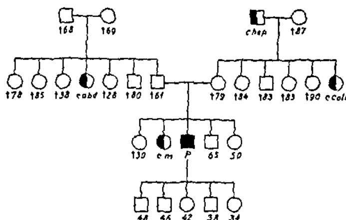
Pedigree 154

PROBAND (Municipal Hospital, service 7, no 435/45)—Widow. Six childbirths Formerly well. When 76 admitted, first to the epidemic service because of "angina" and high fever Hemoglobin 60 %, red cells 2,310,000,

white cells 49,650, myeloblasts 3 %, promyelocytes 3 %, myelocytes 90 %, staff cells 2 %. Wassermann negative. Sternal punctate: Myeloblasts 31 %, promyelocytes 61 %, neutrophile myelocytes 2 %. Died 2 weeks after admission. No necropsy.—Diagnosis: *Acute myelogenous leukemia*

BROTHER.—Died, Feb 15th, 1931, aged 72 of cancer of the esophagus (death certificate).

SISTER.—Died, Dec 24th, 1934, aged 72, of cancer of the stomach (death certificate)



Pedigree 155

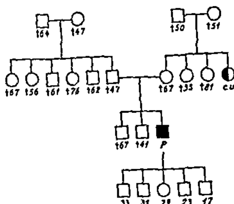
PROBAND (Bispebjerg Hospital, service B, no 5/12/43).—Machine woodworker When 45 found to have diabetes mellitus, for which he got dietary treatment for ten years, after which time he was free from symptoms When 70 admitted owing to persistent fever, cough and dyspnea Examination showed the liver extending 2 cm, the spleen 6 cm, below the costal margin Hemoglobin 49 %, red cells 2,960,000, white cells 15,300, with myeloblasts 50 %, segmented neutrophils 41 %, neutrophile staff cells 1 %, eosinophils 2 %, monocytes 6 % Wassermann negative Observed for 3 months The white cell count 10,000 and 20,000, with 60 to 70 % of myeloblasts Roentgen treatment had no effect. Necropsy (206/43) Spleen 20 × 17 × 7 cm, weight 1050 g—Diagnosis *Acute myelogenous leukemia*

SISTER.—Died, Nov 18th, 1927, aged 56, of cancer of the right breast (death certificate)

FATHER'S SISTER—Died, 1897, aged 69, according to the statements of several relatives, of cancer of the abdomen

MOTHER'S SISTER—Died, Sep 24th, 1912, aged 57, of cancer of the colon (death certificate)

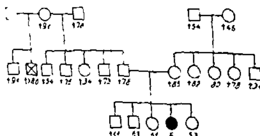
MOTHER'S FATHER—Died, May 3rd, 1894, aged 73 of cancer of the liver (death certificate)



Pedigree 156

PROBAND (Bispebjerg Hospital: service B, no 67/4/43)—Clerk Formerly well When 66 admitted owing to fatigue, dyspnea and smarting tongue. No glossitis, no enlargement of spleen or liver, but gradually there came hemorrhagic diathesis and infiltrations in the skin. Hemoglobin 30 %, red cells 1,460,000, white cells 2,400, promyelocytes 2 %, neutrophile myelocytes 6 %, neutrophile metamyelocytes 4 %, neutrophile staff cells 6 %, segmented neutrophils 12 %, eosinophils 2 %, lymphocytes 68 %. Died 2½ months after the appearance of the first symptoms Necropsy (61/43): The bone marrow hyperplastic, characterised by the large number of promyelocytes—Diagnosis *Acute myelogenous leukemia*

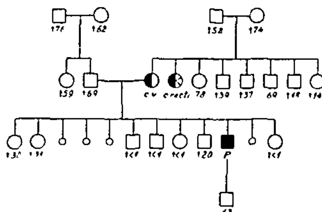
MOTHER'S SISTER—Died, Jan 21st, 1881, aged 38, of cancer of the uterus (death certificate)



Pedigree 157

PROBAND (County Hospital, Gentofte, service F, no 1006/39)—Restaurant-owner Never pregnant When 14 diphtheria, scarlatina and *nephritis* When 57 hemorrhagic diathesis and increasing fatigue, shortly afterwards admitted with severe stomatitis accompanied by difficulty of deglutition, hoarseness and cough No enlargement of lymph nodes, spleen or liver,

Hemoglobin 35 %, red cells 2,610,000, white cells 4,040, myeloblasts 35 % small lymphocytes 53 %, large lymphocytes 3 %, thrombocytes 8,600. Sternal punctate: Myeloblasts 83 %, promyelocytes 3 %, neutrophile myelocytes 3 % Wassermann negative. Died 2 months after admission Necropsy: Spleen 15 × 9 × 6 cm ; leukemic infiltration in liver and spleen —Diagnosis. *Acute myelogenous leukemia*

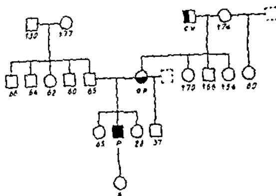


Pedigree 158

PROBAND (St. Luke's Hospital; no. 362/43).—Wholesale merchant Nearly always well until he, when 46, got stomatitis Shortly afterwards admitted owing to epistaxis Examination showed the spleen enlarged, but not extending below the costal margin Hemoglobin 37 %, red cells 2,020,000, white cells 4,960, myeloblasts + promyelocytes 75 %, myelocytes 4 %, segmented neutrophils 8 %, eosinophils 4 %, lymphocytes 9 %. Wassermann negative Died after 5 weeks' illness. No necropsy —Diagnosis: *Acute myelogenous leukemia*

MOTHER —Died, May 3rd, 1923, aged 65, of cancer of the stomach (death certificate)

MOTHER'S SISTER —Died, March 30th, 1939, aged 68, of cancer of the rectum (death certificate)

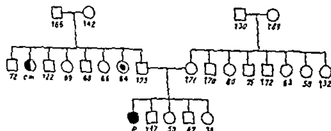


Pedigree 159

PROBAND (County Hospital, Gentofte, service F, no 171/45)—Business manager. When 6 diphtheria, when 11 uncomplicated rheumatic fever, when 20 syphilis (adequately treated, Wassermann afterwards always negative) When 42 *admitted suffering from pains in the joints, fever and hemorrhagic* diathesis No enlargement of liver, spleen or lymph nodes Hemoglobin 49 %, red cells 2,560,000, white cells 208,000, myeloblasts 37 %, myelocytes 57 %, segmented neutrophils 5 % Wassermann negative Leukemic retinitis occurred. Died after at least 2 months' illness Necropsy· Spleen 350 g, liver 28 × 22 × 8 cm, myeloid infiltration in liver, spleen and bone marrow—Diagnosis *Acute myelogenous leukemia*

MOTHER.—Living, aged 72 Has pernicious anemia, ascertained when she was 69 (Frederiksberg Hospital, service E, no 1935/42), and suffers from gastric achylia Hemoglobin 89 %-60 %, color index 1.34-1.54, *after specific* treatment typical reticulocyte response

MOTHER'S FATHER.—Died, Aug 18th, 1888, aged 47, of cancer of the stomach (death certificate)



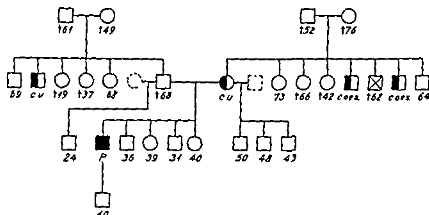
Pedigree 160

PROBAND (Bispebjerg Hospital, service C, no 2/8/36)—Housewife One childbirth When 24 appendectomy, when 39 tonsillectomy When 42 ulceration of the gums Examination did not show any enlargement of spleen or

lymph nodes, but hemoglobin 31 %, red cells 1,600,000, white cells 42,200, myeloblasts (oxydase-positive) 76 %, promyelocytes 2 %, neutrophile myelocytes 6 %, neutrophile staff cells 4 %, segmented neutrophils 3 %, lymphocytes 6 %, thrombocytes 48,000. Wassermann negative Died 1 month after admission No necropsy.—Diagnosis. *Acute myelogenous leukemia*

FATHER'S SISTER—Died, aged 69, having a few years before been operated on for breast cancer (Frederiksberg Hospital; service A, no. 1752/36).

FATHER'S SISTER—Living, aged 64. When younger operated on abroad, after preceding iodine treatment, for struma; photographs from that time show exophthalmus (of which there is no other recorded case in the family) —Diagnosis Graves' disease.



Pedigree 161

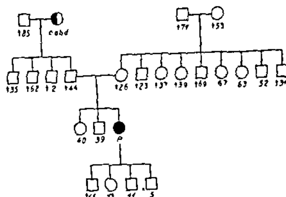
PROBAND (State Hospital, service A, no 427/42)—Milk-cart driver. Formerly well When 34 admitted owing to diarrheas, loss of weight and pain below the left costal margin Examination did not show any marked enlargement of lymph nodes, but the spleen extended 12 cm below the costal margin Hemoglobin 65 %, red cells 3,560,000, white cells 570,000, myeloblasts 4½ %, promyelocytes 10½ %, neutrophile myelocytes 35½ %, eosinophile myelocytes 2½ %, neutrophile metamyelocytes 14 %, neutrophile staff cells 9 %, segmented neutrophils 18 %; thrombocytes 650,000 Wassermann negative Died 2 months after admission Necropsy Leukemic infiltration in spleen, liver, kidneys and pericardium—Diagnosis· *Acute myelogenous leukemia*

MOTHER—Died, March 15th, 1915, aged 36, of uterine cancer (death certificate)

MOTHER'S BROTHER—Died, March 2nd, 1935, aged 60, of cancer of the esophagus (death certificate)

MOTHER'S BROTHER—Died, May 31st, 1931, aged 47, of cancer of the esophagus (death certificate)

FATHER'S BROTHER—Died, Jan 20th, 1944, aged 63, of cancer of the stomach (death certificate)

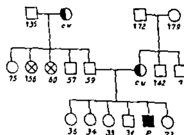


Pedigree 162.

PROBAND (State Hospital, service B, no 372/41)—Housewife Four childbirths When 31 admitted with edemas and hypertension Hemoglobin 50 % Gave, after blood transfusion, birth to a living, healthy male child, but the anemia got more severe, a month later blood examination showed hemoglobin 30 %, red cells 1,520,000, white cells 7,960, myeloblasts 54 %, myelocytes 8 %, neutrophile staff cells 4 %, segmented neutrophils 33 %, thrombocytes 32,000 Sternal punctate Myeloblasts 29 %) promyelocytes 11 %, neutrophile myelocytes 27 %, neutrophile metamyelocytes 7 %, neutrophile staff cells 2 %, segmented neutrophils 6 %, lymphocytes 4 %, erythroblasts 12 % Wassermann negative Died 4 months after admission Necropsy (167/41) Spleen 360 g, massive leukemic infiltration in lymph nodes and kidneys—Diagnosis *Acute myelogenous leukemia*

FATHER'S MOTHER.—Died, 1911, aged 70, after suffering for 6 months from considerable loss of weight, periodic pains in the abdomen and, towards the end, increasing jaundice—Diagnosis Cancer of the abdomen

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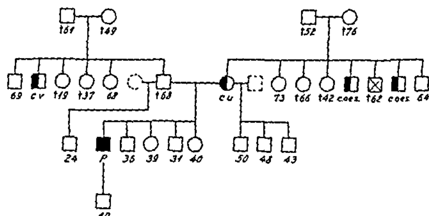
Pedigree 163

PROBAND (Bispebjerg Hospital, service C, no 76/12/40)—Electrowelder When 15 large panaritium When 23 symptoms of increasing anemia, no enlargement of lymph nodes or spleen, but marked hemorrhagic diathesis

lymph nodes, but hemoglobin 31 %, red cells 1,600,000, white cells 42,200, myeloblasts (oxydase-positive) 76 %, promyelocytes 2 %, neutrophile myelocytes 6 %, neutrophile staff cells 4 %, segmented neutrophils 3 %, lymphocytes 6 %; thrombocytes 48,000 Wassermann negative Died 1 month after admission. No necropsy.—Diagnosis: *Acute myelogenous leukemia.*

FATHER'S SISTER—Died, aged 69, having a few years before been operated on for breast cancer (Frederiksberg Hospital; service A, no. 1752/36).

FATHER'S SISTER—Living, aged 64 When younger operated on abroad, after preceding iodine treatment, for struma, photographs from that time show exophthalmus (of which there is no other recorded case in the family). —Diagnosis. Graves' disease.



Pedigree 161

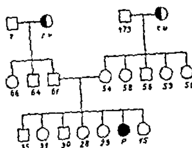
PROBAND (State Hospital, service A, no 427/42)—Milk-cart driver. Formerly well When 34 admitted owing to diarrheas, loss of weight and pain below the left costal margin Examination did not show any marked enlargement of lymph nodes, but the spleen extended 12 cm below the costal margin Hemoglobin 65 %, red cells 3,560,000, white cells 570,000, myeloblasts $4^1/_2$ %, promyelocytes $10^1/_2$ %, neutrophile myelocytes $35^1/_2$ %, eosinophile myelocytes $2^1/_2$ %, neutrophile metamyelocytes 14 %, neutrophile staff cells 9 %, segmented neutrophils 18 %, thrombocytes 650,000 Wassermann negative Died 2 months after admission Necropsy· Leukemic infiltration in spleen, liver, kidneys and pericardium—Diagnosis *Acute myelogenous leukemia*

MOTHER—Died, March 15th, 1915, aged 36, of uterine cancer (death certificate)

MOTHER'S BROTHER—Died, March 2nd, 1935, aged 60, of cancer of the esophagus (death certificate)

MOTHER'S BROTHER—Died, May 31st, 1931, aged 47, of cancer of the esophagus (death certificate)

FATHER'S BROTHER—Died, Jan 20th, 1944, aged 63, of cancer of the stomach (death certificate)

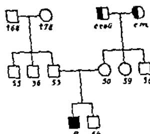


Pedigree 165

PROBAND (County Hospital, Gentofte, service F, no. 993/37) —Daughter of workingman. As child measles and whooping-cough, and in her 7th to 9th year ten times quinsy Shortly afterwards she rather suddenly got markedly fatigued and was admitted with severe hemorrhagic diathesis There was slight, universal enlargement of the lymph nodes, the spleen extended almost to the umbilicus, the liver 3 cm below the costal margin Hemoglobin 61 %, red cells 3,750 000, white cells 686,000, nearly all myeloblasts, with a few myelocytes, thrombocytes 98,000. Died of cerebral hemorrhage 4 days after admission Necropsy· Spleen 380 g; myeloblastic infiltration in bone marrow, kidney and liver —Diagnosis· *Acute myelogenous leukemia*

FATHER'S MOTHER —Died, June 15th, 1932, aged 79, of cancer of the stomach (death certificate)

MOTHER'S MOTHER —Died, Apr 21st, 1909, aged 40, of cancer of the uterus (death certificate)



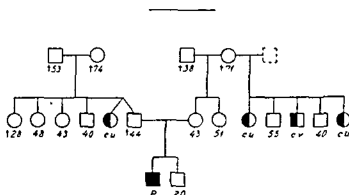
Pedigree 166

PROBAND (Bispebjerg Hospital, service E, no 101/4/30) —Son of engine driver When 3 adenectomy When nearly 4 admitted rather pale and suffering from pain in the abdomen Lymph nodes, spleen and liver slightly enlarged Hemoglobin 47 %, white cells 49,300, lymphoblasts 5 %, lymphocytes 38½ %, neutrophile myelocytes 2 %, neutrophils staff cells 3½ %, segmented neutrophils 5½ %, eosinophils ½ %, basophils 3 %, monocytes 2 % Followed for 2 months, white cell count increasing to 104,000, with

Hemoglobin 33 %, red cells 1,230,000, white cells 4,360, increasing to 16,000, myeloblasts 75 %, promyelocytes 11 %, neutrophile myelocytes 5 %, segmented neutrophils 6 %, lymphocytes 3 %, thrombocytes 5,000. Wassermann negative. Sternal punctate: Myeloblasts 90 %. Died 2 weeks after admission Necropsy: Numerous myeloblasts and myelocytes in bone marrow, spleen and liver.—Diagnosis. *Acute myelogenous leukemia*

MOTHER.—Died, Apr. 28th, 1938, aged 56, of cancer of the uterus (death certificate).

FATHER'S MOTHER —Died, Oct 15th, 1925, aged 75, of cancer of the stomach (death certificate).



Pedigree 164

PROBAND (Municipal Hospital; service 7, no 769/44)—Apprentice. When 2 years old protracted cysteopyelitis. When 17 increasing fatigue, dyspneá and hemorrhagic diathesis Moderate, universal enlargement of the lymph nodes, the liver palpable 8 cm. below the costal margin. Hemoglobin 36 %, red cells 2,000,000, white cells 114,000, myeloblasts 97 %, promyelocytes 1 %, myelocytes 1 %, lymphocytes 1 %, thrombocytes 24,000. Wassermann negative Necropsy (700/44): Leukemic infiltration in lymph nodes, spleen and liver—Diagnosis: *Acute myelogenous leukemia*

FATHER'S SISTER—Died, June 18th, 1932, aged 32, of cancer of the uterus (death certificate)

MOTHER'S HALF-SISTER—Died, Jan 27th, 1925, aged 36, of cancer of the uterus (death certificate)

MOTHER'S HALF-BROTHER—Died, June 15th, 1946, aged 43, of cancer of the stomach (death certificate)

MOTHER'S HALF-SISTER—Died, Oct 31st, 1945, aged 37, of cancer of the uterus (death certificate)

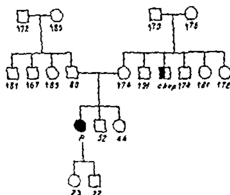
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steadily increasing atoxic goiter When 60 admitted suffering from fever and hemorrhagic diathesis. Hemoglobin 46 %, red cells 2,350,000, white cells 3,080, thrombocytes 21,070 No enlargement of lymph nodes The spleen extending 3 cm below the costal margin Died 3 days after admission, under a large hematemesis Necropsy (393/39) Spleen 19 × 10 × 3 cm, the bone marrow of dirty, greyish color, infiltration of cells resembling myeloblasts in liver and spleen — Diagnosis: Stem-cell leukemia

SISTER — Died, Dec. 2nd, 1940, aged 58, of breast cancer (death certificate)

MOTHER'S SISTER — Died, Oct 31st, 1915, aged 68, of cancer of the stomach (death certificate)

MOTHER'S SISTER — Died, March 8th, 1945, of cancer of the abdomen (death certificate)



Pedigree 169

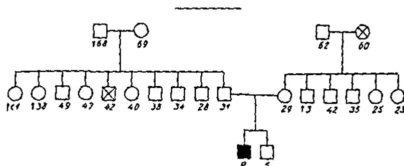
PROBAND (Municipal Hospital, service 3, no 431/44) — Housewife Two childbirths When 53 admitted, having been found to suffer from anemia Many suggillations, no enlargement of lymph nodes; the spleen extending to the midline and the umbilicus Hemoglobin 35 %, red cells 1,700,000, white cells 96,000, large lymphocytes 41 %, small lymphocytes 36 %, stem cells 21 %, thrombocytes 13,000 Wassermann negative Sternal punctate Stem cells 96 % Good effect of roentgen treatment Died 4 weeks after admission Necropsy (224/44) Leukemic infiltration in spleen and liver — Diagnosis *Stem-cell leukemia*

MOTHER'S BROTHER — Died, Feb 21st, 1894, aged 50, of cancer of the liver (death certificate)

myeloblasts 63 %, myelocytes 15 % Wassermann negative No necropsy. —Diagnosis: *Acute myelogenous leukemia.*

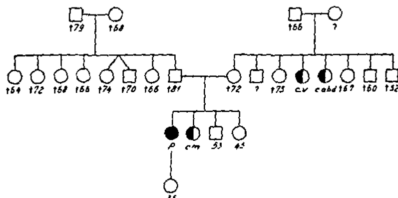
MOTHER'S FATHER.—Died, Apr. 9th, 1933, aged 71, of cancer of the colon (death certificate)

MOTHER'S MOTHER.—Died, Oct. 17th, 1935, aged 74, of breast cancer (death certificate).



Pedigree 167.

PROBAND (Queen Louise's Children's Hospital; no. *329/44*) —*Son of* mail carrier Born at time and throve well When 1 year old measles complicated by bilateral otitis media. A week later he was found smeared all over with "cuprinol" and was admitted because he after this was fatigued and slightly feverish Examination showed microadenitis in the neck, the liver extending 4 cm, the spleen 2 cm, below the umbilicus Hemoglobin 36 %, red cells 1,720,000, white cells 84,400, myeloblasts 19 %, micromyeloblasts 73 %, promyelocytes 3 %, myelocytes 2 %, metamyelocytes 1 %, lymphocytes 2 % Thrombocytes 70,000 Wassermann negative Died after severe hemorrhagic diathesis and necrotic stomatitis had developed Necropsy Spleen and lymph nodes hyperplastic Microscopy confirmed the diagnosis of *acute myelogenous leukemia*

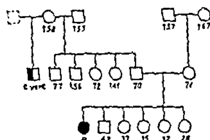


Pedigree 168

PROBAND (Frederiksberg Hospital, service B, no 1876/39) —Housewife One childbirth Several times erysipelas of the face From her 57th year a

cytes 5 %, metamyelocytes 1 %, staff cells 1 %, lymphocytes 2 %, erythroblasts 2½ % Observed for 2 months Wassermann negative. No necropsy —Diagnosis: *Stem-cell leukemia*

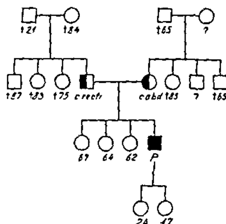
MOTHER'S BROTHER—Died, Aug 20th, 1930, aged 60, of cancer of the sacrum (death certificate)



Pedigree 172

PROBAND (Radium Center; no 15537)—Seamstress. Never pregnant When 20 appendectomy, since her 36th year several attacks of gallstone, when 37 pyelitis, when 42 roentgen castration owing to metrorrhaghias Two years later suddenly very fatigued and pale Examination showed the spleen extending to the costal margin, hemoglobin 22 %, red cells 1,270,000, white cells 92,000, myeloblastic cells 92 %, lymphocytes 4½ % Thrombocytes 65,000 Wassermann negative Sternal punctate Peroxydase-negative, myeloblastic cells 94.7 % lymphocytes 4 % Died 1 month after admission Necropsy (102/40) Spleen 12 × 9 × 4 cm., liver 24 × 16 × 10 cm; no infiltration in liver or kidneys, but the bone marrow hyperplastic, with almost exclusively myeloblastic cells—*Diagnosis: Stem-cell leukemia*

FATHER'S HALF-BROTHER—Died, Sep 24th, 1916, aged 49, of cancer of the stomach (death certificate)

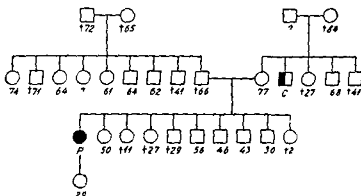


Pedigree 170.

PROBAND (Bispebjerg Hospital; service B, no. 44/2/36) —Saddler Formerly well. When 51 admitted, suffering from extreme fatigue, perspiration, dyspnea and cramps in the calves The spleen palpable 3 cm below the costal margin Hemoglobin 51 %, red cells 2,610,000, white cells 14,900, lymphocytes 27 %, lymphoblasts 68 %, thrombocytes 23,000 Wassermann negative Roentgen treatment without effect. Died after about 4 months' illness. No necropsy —Diagnosis: *Stem-cell leukemia*

FATHER.—Died, Aug 2nd, 1891, aged 45, of cancer of the rectum (death certificate)

MOTHER —Died, Nov 28th, 1930, aged 86, of cancer of the abdomen (death certificate)



Pedigree 171

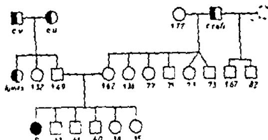
PROBAND (Bispebjerg Hospital, service B, no 66/2/44) —Housewife One childbirth Formerly well When 50 admitted owing to increasing fatigue and pallor. No enlargement of lymph nodes, spleen or liver Hemoglobin 58 %, red cells 2,810,000, white cells 800, thrombocytes 38,400 Sternal punctate rich in cells, hemocytoblasts 30 %, promyelocytes 56 %, myelo-

15 800, stem-cells 98½ %. Died the day after admission Necropsy (294/45): Leukemic infiltration in liver, spleen and bone marrow —*Diagnosis· Stem-cell leukemia*

BROTHER —Living, aged 47 In November 1939 operated on, in St. Elisabeth's Hospital, Copenhagen, for cancer of the rectum

FATHER'S SISTER —Living, aged 70. Ten years ago operated on for breast cancer, one breast being removed, with evacuation of the axilla (Case record not found).

MOTHER S BROTHER —Died, Apr 3rd, 1944, aged 72, of cancer of the pancreas (death certificate)



Pedigree 175

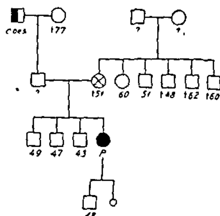
PROBAND (County Hospital, Gentofte, service F. no 553/42) —Clerk Never pregnant When 34 peritonsillar abscess When 41 admitted owing to extreme fatigue shortly afterwards followed by strong menorrhagia, chill and rise of temperature Examination showed moderate enlargement of the lymph nodes in the neck, but no enlargement of liver or spleen Hemoglobin 34 %, red cells 1,600 000, white cells 4,120, 89 % of which are described as lymphocytes Wassermann negative Duration of illness hardly over 4 months Necropsy Spleen 14 × 7 × 3 cm, liver 28 × 18 × 7 cm; the sternal marrow consisting chiefly of myeloblasts and myelocytes, erythropoiesis sparse —Diagnosis *Stem-cell leukemia*

FATHER S SISTER —Died, July 15th, 1936, aged 67, of lymphosarcoma of the right groin with metastases to the organs (death certificate)

FATHER S FATHER —Died, Feb 2nd 1910, aged 62, of cancer of the stomach (death certificate)

FATHER S MOTHER —Died July 23rd, 1912, aged 62, of cancer of the uterus (death certificate)

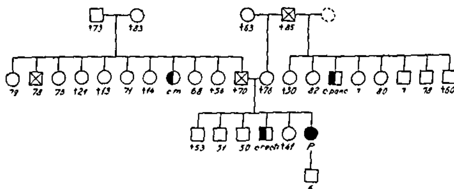
MOTHER S FATHER.—Died, Oct 14th, 1913, aged 81, of cancer of the colon (death certificate)



Pedigree 173

PROBAND (St Elisabeth's Hospital; no 243/43) —Housewife. Two childbirths From 41st to 44th year taenia When 44 admitted with hemoglobin 50 %, red cells 1,480,000, white cells 2,600, myelocytes 3 %, neutrophile metamyelocytes 3 %, neutrophile staff cells 4 %, segmented neutrophils 7 %, lymphocytes 51 %, atypical forms 23 % Wassermann negative. In the course of three weeks 6 sternal punctures were done, the punctates showing increasing shift to the left of the myeloid series and decreasing erythropoiesis The last examination, 1 month before the patient died, showed hemocytoblasts + myeloblasts 79 %, neutrophile myelocytes 10 %, eosinophile myelocytes 4 %, basophile myelocytes 1 % The white cell count slowly rising to 25,000 Towards the end thrombocytes 10,000 Died 6 weeks after admission No necropsy —Diagnosis *Stem-cell leukemia*

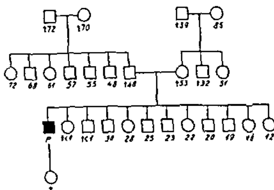
FATHER'S FATHER —Died, June 5th, 1929, aged 76, of cancer of the cardia (death certificate).



Pedigree 174

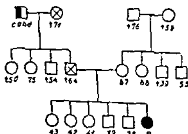
PROBAND (State Hospital, service A, no 665/45) —Housewife One childbirth Always well until she, when 43, was admitted owing to fever and hemorrhagic diathesis Hemoglobin 22 %, red cells 1,240,000, white cells

suffered from increasing fatigue Examination showed numerous, up to almond-sized lymph nodes in the neck, and the spleen extending 2 cm below the costal margin. Hemoglobin 74 % (falling), red cells 3,110,000, white cells 70,000, stem cells 81 %, thrombocytes 19,000 The sternal punctate consisted almost exclusively of mononuclear cells (? myeloblasts). Wassermann negative Died 1 month after admission No necropsy —Diagnosis *Stem-cell leukemia*



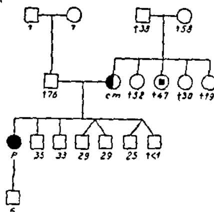
Pedigree 178

PROBAND (Blegdam Hospital, no 2711/44) —Workingman Formerly well When 30 admitted with "angina". Right tonsil gangrenous, in the groin a few almond-sized lymph nodes Hemoglobin about 50 % *Differential blood count* Myelocytes 78 %, segmented neutrophils 2 %, lymphocytes 20 % Sternal punctate: Myeloblasts (?) 96 %, Wassermann negative Necropsy defective, no microscopy of organs —Diagnosis· *Stem-cell leukemia*



Pedigree 179

PROBAND (Frederiksberg Hospital, service B, no 1773/42) —Kindergarden-mistress Never pregnant When 26 operations for removal of ovarian cysts and appendix Six months later "angina", persistent fever, moderate enlargement of lymph nodes, and the spleen extending to the costal margin. Hemoglobin 41 %, red cells 2,920,000, white cells 37,760, myeloblasts (?)

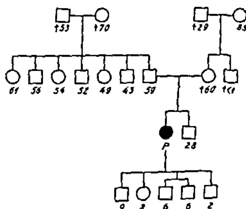


Pedigree 176

PROBAND (County Hospital, Gentofte; service C, no 1301/41).—Housewife. One childbirth. When 22 pylorogastritis When 33 admitted with high fever and tonsils covered with necrotic membranes No splenomegaly. Hemoglobin 53 %, red cells 1,500,000, white cells 14,400, myeloblasts 82 %, lymphocytes 17 %, thrombocytes 28,000 Bunnel's test and Wassermann negative Sternal punctate: Myeloblasts 97 %. Died 2 weeks after admission Necropsy: Liver 25 × 20 × 8 cm, spleen 17 × 9 × 4 cm, leukemic infiltration in liver, spleen and bone marrow.—Diagnosis· *Stem-cell leukemia*

MOTHER —Died, July 31st, 1932, aged 55, of breast cancer (death certificate)

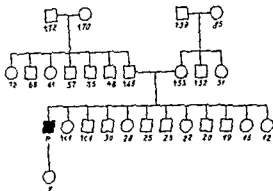
MOTHER'S SISTER.—Died, June 16th, 1932, aged 47, of cardiac disease Had myxedema, stated to have been typical, but the symptoms disappeared after treatment with thyreoidin (Hospital, Tarm)



Pedigree 177

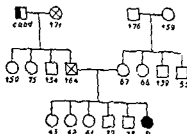
PROBAND (Radium Center, no 35120)—Housewife Five childbirths When 29 angina and arthralgia, and had her tonsils removed When 31 she suddenly got pain in both lower extremities, hemorrhagic diathesis and

suffered from increasing fatigue Examination showed numerous, *up to* almond-sized *lymph nodes* in the neck, and the spleen extending 2 cm below the costal margin Hemoglobin 74 % (falling), red cells 3,110,000, white cells 70,000, stem cells 81 %, *thrombocytes 19,000*. The sternal *punctate* consisted almost exclusively of mononuclear cells (? myeloblasts). Wassermann negative Died 1 month after admission No necropsy.—Diagnosis *Stem-cell leukemia.*



Pedigree 178

PROBAND (Blegdam Hospital, no 2711/44) —Workingman Formerly well When 30 admitted with "angina" Right tonsil gangrenous, in the groin a few almond-sized lymph nodes Hemoglobin about 50 % Differential blood count Myelocytes 78 %, segmented neutrophils 2 %, lymphocytes 20 %. Sternal punctate Myeloblasts (?) 96 %. Wassermann negative *Necropsy* defective, no microscopy of organs —Diagnosis *Stem-cell leukemia.*

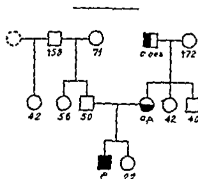


Pedigree 179

PROBAND (Frederiksberg Hospital, service B, no 1773/42) —Kindergarden-mistress Never pregnant. When 26 operations *for removal of ovarian* cysts and appendix Six months later "angina", persistent fever, moderate enlargement of lymph nodes, and the spleen extending to the costal margin Hemoglobin 41 %, red cells 2,920,000, white cells 37,760, myeloblasts (?)

97 %, segmented neutrophils 2 %, lymphocytes 1 %; thrombocytes 14,900. Wassermann negative Died 6 years after admission, with high fever and hemorrhagic diathesis No necropsy—Diagnosis: *Stem-cell leukemia*

FATHER'S FATHER—Died, Jan. 14th, 1894, according to statements of several relatives, of cancer of the abdomen.

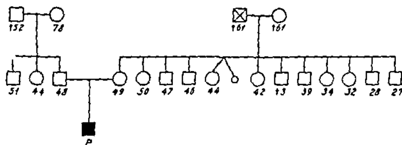


Pedigree 180

PROBAND (Municipal Hospital; service 1, no 1349/42)—Messenger When 15, and again when 19, herniotomy. When 25 increasing fatigue, loss of weight, perspiration and fever; at admission left-side exudative pleurisy, the liver palpable 3 cm. below the costal margin Wassermann negative Died 22 days after admission. Necropsy (486/42) Spleen 12 × 7 × 3 cm, liver 29 × 17 × 8 cm; leukemic infiltration in liver, kidney, pancreas and mesentery—Diagnosis: *Stem-cell leukemia*

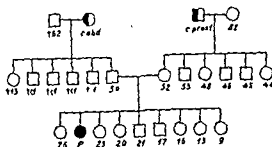
MOTHER—Died, March 25th, 1934, aged 38, of pernicious anemia (death certificate). She died in hospital, but the case record not found

MOTHER'S FATHER.—Died, Nov. 5th, 1923, aged 50, of cancer of the esophagus (death certificate)



Pedigree 181

PROBAND (*Sundby Hospital, service M, no 1985/44*)—*Clerk* Since childhood tendency to corpulence and obstipation When 19 jaundice When 23 admitted with abdominal symptoms and aggravation of the obstipation No enlargement of lymph nodes, spleen or liver, the tonsils hyperplastic Hemoglobin 79 %, white cells 21,000, with myeloblasts (?) 95 %, lymphocytes 5 % Wassermann negative Died 3 days after admission No necropsy —Diagnosis: *Stem-cell leukemia*

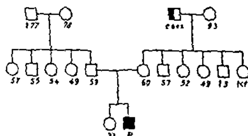


Pedigree 182.

PROBAND (Central Hospital for Frederiksborg County, Hillerod: med service, no 358/43)—Nursemaid Never pregnant. When 21 appendicitis and 3 times peritonsillar abscess When 23 ulorrhagia, considerable hyperplasia of the tonsils and moderate, universal enlargement of the lymph nodes No enlargement of spleen or liver Hemoglobin 48 %, red cells 1,830,000, white cells 85,400 (increasing to 138,000); nearly 100 % described as lymphocytes Thrombocytes about 900 Bunnell's test and Wassermann negative Died 20 days after admission No necropsy—Diagnosis *Stem-cell leukemia.*

FATHER'S MOTHER—Died, July 21st, 1898, aged 39, *according to statements* of several relatives, of cancer of the abdomen

MOTHER'S FATHER—Died, May 24th, 1942, aged 70, *of cancer of the* prostate (death certificate)

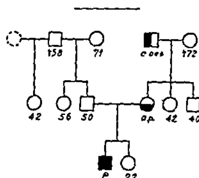


Pedigree 183

PROBAND (Radium Center, no. 27080)—Clerk. When 19 appendectomy When 20 hospitalised with the diagnosis Infectious mononucleosis Afterwards well until he, when 21, suddenly became feverish, with increasing fatigue, dyspnea, perspiration and hemorrhagic diathesis Examination showed the tonsils very large but without coating, the lymph nodes were not enlarged, but the spleen extended 3 cm below the costal margin. Hemoglobin 43 %, red cells 2,140,000, white cells 176,000, stem-cells 99 % Sternal punctate Stem-cells 87 % Thrombocytes 73,000 Wassermann negative. Bunnell's test Agglutination in 2 tubes Died 2 weeks after admission No necropsy—Diagnosis *Stem-cell leukemia*

97 %, segmented neutrophils 2 %, lymphocytes 1 %; thrombocytes 14,900. Wassermann negative. Died 6 years after admission, with high fever and hemorrhagic diathesis. No necropsy.—Diagnosis: *Stem-cell leukemia.*

FATHER'S FATHER.—Died, Jan. 14th, 1894, according to statements of several relatives, of cancer of the abdomen.

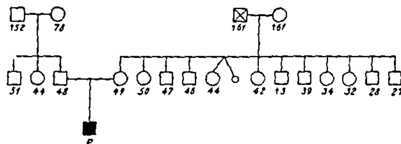


Pedigree 180

PROBAND (Municipal Hospital, service I, no 1349/42)—Messenger When 15, and again when 19, herniotomy. When 25 increasing fatigue, loss of weight, perspiration and fever, at admission left-side exudative pleurisy, the liver palpable 3 cm below the costal margin Wassermann negative Died 22 days after admission Necropsy (486/42) Spleen 12 × 7 × 3 cm, liver 29 × 17 × 8 cm, leukemic infiltration in liver, kidney, pancreas and mesentery—Diagnosis: *Stem-cell leukemia.*

MOTHER.—Died, March 25th, 1934, aged 38, of pernicious anemia (death certificate) She died in hospital, but the case record not found

MOTHER'S FATHER—Died, Nov 5th, 1923, aged 50, of cancer of the esophagus (death certificate)



Pedigree 181

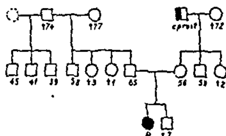
PROBAND (Sundby Hospital, service M. no 1985/44)—Clerk Since childhood tendency to corpulence and obstipation. When 19 jaundice When 23 admitted with abdominal symptoms and aggravation of the obstipation No enlargement of lymph nodes, spleen or liver, the tonsils hyperplastic Hemoglobin 79 %, white cells 21,000, with myeloblasts (?) 95 %, lymphocytes 5 % Wassermann negative Died 3 days after admission No necropsy —Diagnosis: *Stem-cell leukemia*

midline Hemoglobin 45 %, red cells 3,000,000, white cells 9,100, stem-cells 98 %; thrombocytes 4,600. Wassermann negative. Died 1 month after admission Necropsy (116/36): Leukemic infiltration in spleen, liver and kidneys — Diagnosis: Stem-cell leukemia.

FATHER'S SISTER.—Living, aged 62 When 41 operated on for cancer of the rectum (Bispebjerg Hospital, service A, no. 127/3/23)

FATHER'S SISTER—Living, aged 56 When 29 operated on for Graves' disease Before the operation she had struma and exophthalmus, suffered from insomnia, was nervous and thin; since the operation she has been well

FATHER'S FATHER—Died, March 22nd, 1926, aged 76, of cancer of the rectum (death certificate)

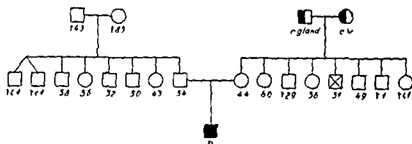


Pedigree 186

PROBAND (Blegdam Hospital, no 566/44)—Daughter of head clerk When 10 appendectomy When 15 admitted suffering from fever, pain when swallowing, and moderate enlargement of the lymph nodes in the neck. No enlargement of the spleen or liver Hemoglobin 29 %, red cells 1,330 000, white cells 3,900 (falling to 590), small lymphocytes 40 %, stem-cells 59 %. Sternal punctate Stem-cells (? myeloblasts) about 99 % Bunnell's test and Wassermann negative Died 16 days after admission Necropsy: Leukemic infiltration in liver, spleen and bone marrow—Diagnosis Stem-cell leukemia

MOTHER'S FATHER.—Died, June 22nd, 1928, aged 61, of cancer of the prostate (death certificate)

MOTHER'S FATHER.—Died, Aug. 20th, 1919, aged 63, of cancer of the esophagus (death certificate).

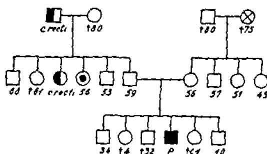


Pedigree 184

PROBAND (County Hospital, Gentofte, service C, no. 1310/41).—Son of steward Formerly well *When 17 abscess in the back of the neck, with* inflammation of the glands in the neck, and shortly afterwards hemorrhagic diathesis, severe stomatitis and hyperplasia of the tonsils The liver palpable 2 cm., the spleen 3 cm., below the costal margin Hemoglobin 60 %, red cells 2,640,000, white cells 206,200, stem cells 80 %, promyelocytes 3 %, *lymphocytes 13 % Wassermann negative Died 24 months after admission.* Necropsy. Spleen 1070 g, liver 29 × 20 × 10 cm.; microscopy of lymph nodes, spleen, liver and bone marrow showed typical leukemia —Diagnosis *Stem-cell leukemia*

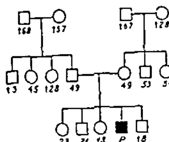
MOTHER'S FATHER.—Died, Jan 3rd, 1940, aged 75, of cancer of the glands in the neck (Radium Centre, Copenhagen, no 14135)

MOTHER'S MOTHER —Died, Apr 12th, 1916, aged 52, of cancer of the stomach (death certificate).



Pedigree 185

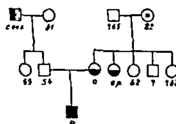
PROBAND (Municipal Hospital; service 2, no 143/2/36) —Electrician's apprentice As child diphtheria, ileus and "abscess in the lung" When 15 appendectomy. When 17 hospitalised because he after an "influenza" continued *to be feverish* and fatigued Examination showed universal enlargement of the lymph nodes, which in some places were as large as a small apple; the liver extended 8 cm below the costal margin, the spleen to the



Pedigree 189.

PROBAND (State Hospital, service G, no 178/45)—Son of cement-founder Born at term. When 6 scarlatina and fracture of one leg When 9 recurrent otitis media and erythema nodosum (Mantoux negative). When 10 adenoids removed. Shortly afterwards universal enlargement of lymph nodes, and spleen palpable 4 cm below the costal margin Hemoglobin 90 %, red cells 5,880,000, white cells 47,800, of which 82 % described as lymphocytes (peroxydase-negative) Sternal punctate. Stem-cells (most resembling myeloblasts) 92 %. No effect of roentgen treatment. The white cell count rose and was towards the end 160,800 Necropsy (142/45): Spleen 900 g, liver 27 × 20 × 7 cm; leukemic infiltration in lymph nodes and liver —Diagnosis Stem-cell leukemia

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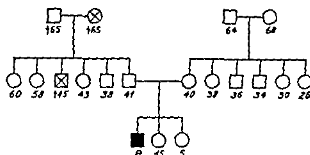
Pedigree 190

PROBAND (Childrens Hospital, Fuglebakken, no 33/37)—Daughter of barber Born at term, weighing 3,300 g When 4 adenoids removed, when 6 measles When 6½ vaccinated against variola, and shortly afterwards she got swollen lymph nodes in the neck. When 7 admitted with high fe...

... negative Was given roentgen treatment, but died shortly afterwards No necropsy —Diagnosis· *Stem-cell leukemia*

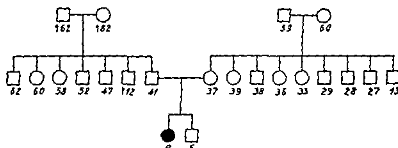
MOTHER—Living, aged 51, suffers from gastric achylia, glossitis and simple anemia (hemoglobin, despite iron therapy, about 80 %)

MOTHER S SISTER—Died, Oct 11th, 1930, of pernicious anemia, 7 hours



Pedigree 187

PROBAND (County Hospital, Gentofte, service F, no 209/39)—Son of workingman When 9 admitted with severe hemorrhagic diathesis Moderate enlargement of lymph nodes in the neck, no enlargement of the spleen. Hemoglobin 48 %, red cells 2,080,000, white cells 420,000, stem-cells 88 % Thrombocytes 73,000 Observed for 3 months, during which time the condition remained more or less unchanged. No necropsy—Diagnosis: *Stem-cell leukemia.*



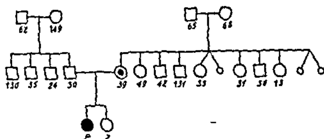
Pedigree 188

PROBAND (State Hospital, service A, no 456/45)—Daughter of tailor. Formerly well, except for uncomplicated measels When 9 she suddenly got pains in the right calf and foot, which became blueish Marked enlargement of the liver Hemoglobin 90 %, red cells 4,500,000, white cells 6,000, stem-cells 94 %, neutrophile staff cells 3½ % Sternal punctate Stem-cells 92 %, thrombocytes 14,600 Wassermann negative Died 12 days after admission. Necropsy (456/45): Leukemic infiltration in the liver and the inferior vena cava—Diagnosis *Stem-cell leukemia*

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cells 2,880,000, white cells 960,000, nearly all myeloblastic, thrombocytes 20,000 Wassermann negative Died 12 days after admission. No necropsy — Diagnosis: *Stem-cell leukemia.*

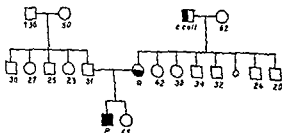
FATHER'S MOTHER — Died, 1922, aged 42, of uterine cancer (bloody discharges from the vagina, treated with roentgen, case record not found).



Pedigree 193

PROBAND (Radium Center, no 28287) — Daughter of book-keeper Formerly well, developed normal When 4 "bronchitis", swollen face and neck, and increasing dyspnea Walnut-sized lymph nodes and phlebostasis in the neck and polypnea The spleen palpable 3 cm below the costal margin The mediastinal shadow about three-fourths of the breadth of the torax Hemoglobin 87 %, red cells 4,990,000, white cells 42,000, myeloblasts 6 %, neutrophile myelocytes 10½ %, neutrophile staff cells 11½ %, segmented neutrophils 44½ %, eosinophils 3 %, mononuclears 23½ % Wassermann negative. Under roentgen treatment the mediastinal shadow diminished somewhat. The patient died after about 4 months' illness Necropsy (131/42): Leukemic infiltration in pericardium, myocardium, kidneys, ovaries, spleen (240 g) and liver (900 g) — Diagnosis *Stem-cell leukemia*

MOTHER — Living, aged 39 When 17 struma, high basal metabolic rate and loss of weight, but the symptoms disappeared in the course of 3 years without treatment — Diagnosis Graves disease



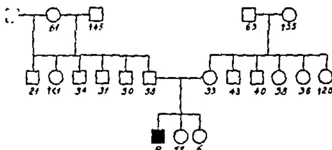
Pedigree 194

PROBAND (County Hospital, Gentofte, service A, no 1030/42) — Son of workingman Born at term When 1 year old rickets When 4 admitted with

after being admitted, moribund, to hospital in Korsor. (Hemoglobin 16 %, red cells 580,000 Blood smear preparation showed distinct aniso-poikilocytosis, some normoblasts and a few megaloblasts; white cells normal).

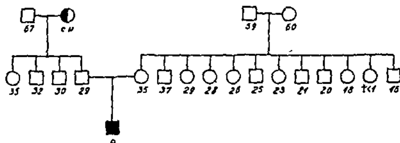
MOTHER'S MOTHER.—Living, aged 82. Has myxedema (Municipal Hospital, Copenhagen; med. policlinic· *Basal metabolic rate 78-87 %. Thyroidin* given with good effect, whereupon the flat T of the electrocardiogram got higher).

FATHER'S FATHER.—Died, Apr 10th, 1938, aged 67, of cancer of the esophagus (death certificate).



Pedigree 191.

PROBAND (County Hospital, Gentofte, service F, no 1387/38)—Son of brasier. Born at term. Formerly well When 6 years old admitted on account of hepatomegaly Universal enlargement of the lymph nodes, up to pea-size. The liver extending 5 cm, the spleen 8 cm, below the costal margin Marked *hemorrhagic diathesis. Hemoglobin rapidly falling to about 20 %, white* cells about 600,000, nearly all stem-cells Thrombocytes 13,000 Died after about 1 month's illness No necropsy—Diagnosis *Stem-cell leukemia.*

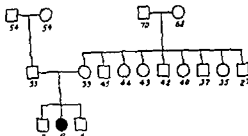


Pedigree 192

PROBAND (Queen Louise's Children's Hospital, no 1/43)—Son of workingman. When 4 whooping-cough and mumps When 5 varicella and rubeola, when 6 measles. After the latter he continued tired, with periodical attacks of fever, and when he further got hematuria and edemas he was hospitalised Examination showed universal enlargement of the lymph nodes, up to hazelnut-size, ulorrhagia, and the spleen extending 5 cm below the costal margin, the border of the liver to the iliac crest Hemoglobin 69 %, red

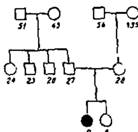
costal margin Hemoglobin 28 %, red cells 1,550,000, white cells 14,460, stem-cells 89 %, small lymphocytes 10 % Wassermann negative Died 3 weeks after admission Necropsy. Leukemic infiltration in the spleen, liver and lymph nodes—Diagnosis: *Stem-cell leukemia*

FATHER'S MOTHER—Died, Dec. 29th, 1919, according to the statements of relatives, of cancer of the liver.



Pedigree 197.

PROBAND (Radium Center, no 29193)—Daughter of bricklayer Normally developed and formerly well When $3^1/_2$ years old enlargement of the lymph nodes in the neck, the spleen palpable 2 cm. below the costal margin Hemoglobin 78 %, red cells 3,810,000, white cells 4,120, lymphocytes 68 % (among which many atypical) Wassermann negative Declined gradually despite roentgen treatment and blood transfusions, and died after 10 months' observation, during which time the leukocyte count was constantly under 10,000, but with about 40 % of stem-cells—Diagnosis *Stem-cell leukemia*



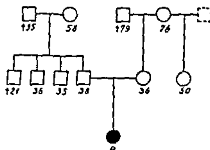
Pedigree 198

PROBAND (Frederiksberg Hospital, service E, no 1665/42)—Daughter of window-cleaner Born at term When 2 tonsillary angina and symptomatic diarrhea, after that time always fatigued When $2^1/_2$ admitted on account of epistaxis Examination showed large suggillations, moderate, universal enlargement of the lymph nodes, no enlargement of the spleen Hemoglobin 34 %, red cells 2,210,000, white cells 3,760, small lymphocytes 89 %, segmented neutrophils 11 %, thrombocytes 70,000 *Sternal* puncture: Myeloblasts (?) 90 % The parents wished the child discharged, and she died a few days later at home—Diagnosis *Stem-cell leukemia*

pains in the right tibia Examination showed enlarged lymph nodes, the size of hazelnut-kernels, in the axillae, and the spleen extending 4 cm. below the costal margin Hemoglobin 60 %, white cells 22,640, lymphocytes (?) 94 %. Wassermann negative Sternal punctate· Lymphoblastic cells 99½ %, erythropoiesis very sparse. Died at home 1 month after admission—Diagnosis: *Stem-cell leukemia.*

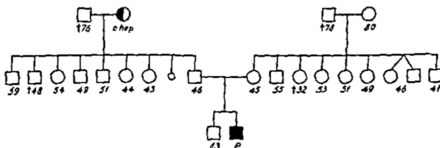
MOTHER—Living, aged 28. Has recurrent, simple anemia (lowest hemoglobin rate about 60 %). Iron therapy used with good effect.

MOTHER'S FATHER—Died, Feb 22nd, 1940, aged 62, of cancer of the sigmoid (death certificate)



Pedigree 195

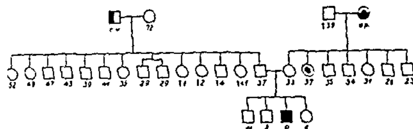
PROBAND (Sundby Hospital; service F, no. 178/44)—Daughter of university lecturer Born at term and throve well When 1 year old acetylic acid poisoning When 4 whooping-cough, a month later admitted with fever and hemorrhagic diathesis The lymph nodes hazelnut-sized, no enlargement of spleen or liver; fauces normal Hemoglobin 60 %, red cells 3,050,000, white cells 14,560, increasing to 53,000; stem-cells about 90 % Wassermann negative Observed for 2 months Necropsy Stem-cell infiltration in the liver.—Diagnosis *Stem-cell leukemia*



Pedigree 196

PROBAND (County Hospital, Gentofte, service F, no 726/41).—Son of electrician. Born at term When 3 varicella. When nearly 4 admitted with frequent loose, often slimy stools, hemorrhagic diathesis, lymph nodes in all regions pea-sized, the spleen extending 5 cm, the liver 3 cm, below the

temperature about 40° C. and "angina", coryza, cough, hyperplasia of the tonsils and rhinopharyngitis The lymph nodes in the neck were slightly enlarged Hemoglobin 32 %, red cells 1,330,000, white cells 3,320, lymphocytes 98 %; thrombocytes 21,000 Bleeding time 90 minutes Wassermann negative Died 1 month after admission White cell count shortly before death 8,360, nearly all stem-cells No necropsy—Diagnosis. *Stem-cell leukemia*



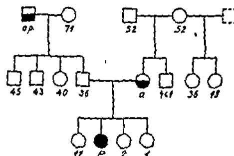
Pedigree 201

PROBAND (Radium Center, no 24805)—Son of mechanic. Born at term and throve well until he, when 2 years old, was admitted *suffering from fever* Examination showed the lymph nodes of all regions slightly enlarged and the liver extending 3 cm below the costal margin, the spleen to the left iliac fossa and the umbilicus Hemoglobin 48 %, red cells 2,240 000, white cells 114,160, stem-cells 85 % Died at home after 2 months' illness—Diagnosis *Stem-cell leukemia*

FATHER'S FATHER.—Died, Dec 30th, 1921, aged 41, of cancer of the stomach (death certificate)

MOTHER'S MOTHER—Died, Dec 15th, 1929, of pernicious anemia (County Hospital, Aarhus, no 1027/29) Admitted *for paresthesias of fingers* and toes, and diarrheas Examination showed struma, basal metabolic rate 173 % (good effect of strumectomy) and gastric achylia Hemoglobin 40 %, color index 1 10, moderate splenomegaly, after liver therapy typical increase of the reticulocyte count The necropsy bore out the diagnosis

MOTHER'S SISTER—Living, aged 37 When 35 operated on for Graves' disease (Finsen Institute, Copenhagen med service, no 13494)

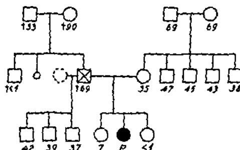


Pedigree 199.

PROBAND (*Children's Hospital, Fuglebakken, no. 297/44*).—Daughter of workingman Born at term, normally developed When 1 year old whooping-cough When 2 admitted on account of symptoms of coxitis after a fall Examination showed sugillations, moderate, universal enlargement of the lymph nodes and the spleen extending 6 cm, the liver 4 cm, below the costal margin Hemoglobin 48 %, falling to 25 %; red cells 2,380,000, white cells 6,960, large lymphocytes 56 %, small lymphocytes 26 %, neutrophile myelocytes 4 %, neutrophile staff cells 1 %, segmented neutrophils 7 %; thrombocytes 79,000 Wassermann negative Died 1 month after admission Necropsy Leukemic infiltration in liver, kidneys and bone marrow.—*Diagnosis: Stem-cell leukemia*

MOTHER.—Living, aged 31 Her hemoglobin rate has for some unknown cause repeatedly been low (every winter about 60 %), but iron therapy has always had good effect.

FATHER'S FATHER.—Living, aged 74. Suffers from pernicious anemia, for which he has for 3 years been given specific treatment with good result, while iron therapy never has had any effect After 2 months' suspension of the treatment a few megaloblasts were found in the bone marrow, besides he suffers from gastric achylia (Examined by the author)

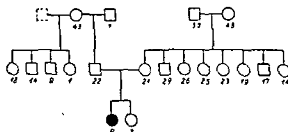


Pedigree 200

PROBAND (Queen Louise's Children's Hospital, *no* 799/44).—Daughter of army officer. Born at term and throve well until she when 2 years old, got feverish and her eyelids swollen Three weeks later admitted with

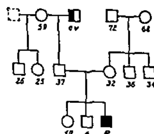
lations, slight, universal enlargement of the lymph nodes and the spleen extending 4 cm, the liver 2 cm, below the costal margin. Hemoglobin 42 %, red cells 2,430,000, white cells 241,000, nearly all stem-cells Died 2 days after admission Necropsy (227/44). Leukemic infiltration in lymph nodes, liver and spleen.—Diagnosis. *Stem-cell leukemia.*

PATERNAL GRANDFATHER'S MOTHER.—Died, aged 73, of bulbar paralysis Had been suffering from myasthenia gravis and pernicious anemia; the first blood examination (10 years before death) showing hemoglobin 25 %, red cells 1,350,000, color index 0.93, and considerable anisocytosis with many macrocytes, besides which gastric achylia was demonstrated After treatment with liver extract the hemoglobin rate had risen to 97 % (Dr *Iversen's* clinic)



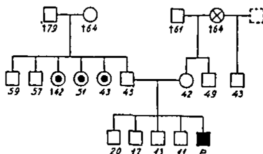
Pedigree 204.

PROBAND (Queen Louise's Children's Hospital, no 1057/42)—Daughter of brewery workman Born at term, breast fed and throve well until she, when 4 months old, got whooping-cough When 6 months old she was admitted with cutaneous abscess and got suppurative otitis media When 2 admitted again, in very poor state, with pneumonia and severe anemia Hemoglobin 34 %, red cells 1,360 000, white cells about 400,000, stem-cells 99 %, myelocytes 1 % Died 24 hours after admission No necropsy—Diagnosis *Stem-cell leukemia*



Pedigree 205

PROBAND (Children's Hospital, Fuglebakken, no 701/44)—Son of lithographer Born at term, breast-fed, normally developed, and well until he,



Pedigree 202

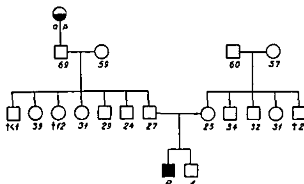
PROBAND (County Hospital, Gentofte, service B, no 1813/39)—Son of carpenter. Born at term. When 10 months old whooping-cough, when 16 months old admitted with edemas in the face, "angina" and hemorrhagic diathesis Hemoglobin 56 % (falling to 33), red cells 3,000,000, white cells 101,600, lymphocytes 40 %, stem-cells 57 %. Moro and Wassermann negative The temperature varying, the white cell count rising to 172, with 76 % of stem-cells. Duration of the illness about 1 month Necropsy Spleen 8 × 6 × 4 cm, the lymphatic tissue hyperplastic—Diagnosis *Stem-cell leukemia*

FATHER'S SISTER—Died, Nov. 15th, 1933, aged 42, after a psychosis *When younger struma, exophthalmus and loss of weight, all of which* symptoms had, however, eventually receded spontaneously.

FATHER'S SISTER—Living, aged 51 Had, when 32, precisely the same symptoms as her sister (a photograph shows typical hyperthyroidism), but is now well

FATHER'S SISTER—Living, aged 43 When 20 roentgen-treated for Graves' disease, presenting for a time the same symptoms as her sisters, but is now well

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Pedigree 203

PROBAND (Frederiksberg Hospital, service B, no 846/44)—Son of confidential clerk. Born at term When 1 year old pneumonia, when 14 months cough, fever, diarrheas and a few vomitings Examination showed suggil-

SUMMARY

Introduction

The author's motives for undertaking the study, and its object

Chapter I

1. The statistical genealogic method is used, and the extent of the material defined as regards the categories of relatives included and the diseases in the families about which information was particularly sought.

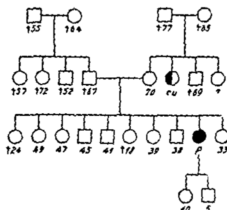
2 The stated cancer diagnoses have been controlled as far as possible and have for 427 cases been verified with a certainty of 92 per cent, while of 687 persons stated not to be affected with cancer 4 were found to have the disease

3 The definition and various types of leukemia are mentioned. Inquiries were made of 310 patients with leukemia, and about the families of 209 of them sufficient data were obtained. It is shown that these 209 probands were representative of the disease as regards its different types, sex- and age incidence

The difficulty of obtaining a serviceable control material is mentioned The control comprises the relatives of 200 sound probands, and it is shown that there is good agreement between the age distribution of 3641 relatives of these and 4041 relatives of the leukemia probands

when 8 months old, was admitted with hemorrhagic diathesis and fever. The spleen and liver extended 2 cm. below the costal margin. Hemoglobin 40 %, red cells 1,950,000, white cells 6,800, stem-cells 92 %, segmented neutrophils 4 %, eosinophils 2 %, basophils 2 %. Died the day after admission. Necropsy: Enormous leukemic infiltration of spleen, liver and kidneys; the spleen 11 × 5 × 3 cm., the kidneys 10 × 5 × 3 cm, the liver very large.—Diagnosis: *Stem-cell leukemia*

FATHER'S FATHER.—Died, Aug 7th, 1928, of cancer of the stomach (death certificate)



Pedigree 206

PROBAND (Bispebjerg Hospital, service B, no 98/5/43).—Housewife Two childbirths As child scarlatina and iridocyclitis When 33 admitted for metrorrhagia and excochleation of the uterus performed, but as her hemoglobin rate was low, she was transferred to the medical service. Examination showed pea-sized lymph nodes in the neck and marked stomatitis with edema of the mucosa. No enlargement of the spleen Hemoglobin 43 %, red cells 1,630,000, white cells 3,200, segmented neutrophils 34 %, monocytes 26 %, lymphocytes 40 %, thrombocytes 139,000 Wassermann negative. *Sternal punctate Considerable hyperplasia, with many monocytes, plasma cells and reticulocytes Gradually the white cell count rose to about 2,000, with 15-20 % of monocytes Duration of the illness at least 6 months Necropsy: Spleen 20 × 12 × 4 cm., liver 31 × 22 × 8 cm, the bone marrow greyish*.—Diagnosis: *Stem-cell leukemia*

MOTHER'S SISTER.—*Died, Jan 6th, 1933, aged 66, of cancer of the uterus (death certificate)*

SUMMARY

Introduction

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2 The stated cancer diagnoses have been controlled as far as possible and have for 427 cases been verified with a certainty of 92 per cent, while of 687 persons stated not to be affected with cancer 4 were found to have the disease.

3 The definition and various types of leukemia are mentioned Inquiries were made of 310 patients with leukemia, and about the families of 209 of them sufficient data were obtained. It is shown that these 209 probands were representative of the disease as regards its different types, sex- and age incidence.

The difficulty of obtaining a serviceable control material is mentioned The control comprises the relatives of 200 sound probands, and it is shown that there is good agreement between the age distribution of 3641 relatives of these and 4041 relatives of the leukemia probands.

Chapter II

1. The available communications in the literature, about familial occurrence of leukemia, are reviewed critically, with the result that 26 observations of at least two patients with leukemia in the same family are accepted as authentic. They make it probable that hereditary factors play a part in the production of the disease, but are not convincing evidence of it being the case.

2. From the investigation of the pedigrees of the 209 patients with leukemia, the familial incidence of the disease is estimated to be at least 8 1 per cent.

Several types of leukemia may occur in the same family. It is shown that the relative frequency with which they occur is the same for the familial cases as for the disease in general. As it furthermore cannot be demonstrated that the multiple occurrence in the individual family, is usually confined to some particular type, the author believes that leukemia genetically is a morbid entity.

Leukemia is a matter of chromosomal inheritance. Leukemia as such is not inherited; the author believes that it is a question of inherited disposition to the disease. Simple dominance or recessivity may be excluded It may possibly be a question of failing dominance or polymeria.

Sex-limitation can be excluded, sex-linkage has not been demonstrated.

It is shown that familial cases of chronic lymphogenous leukemia manifest themselves earlier than it is otherwise usual for this type of the disease. Something similar seems to be the case,—though it cannot be proved with statistical certainty,—with chronic myelogenous and acute leukemia. Members of a sibship oftenest become liable at approximately the same age, and also among more distantly related members of a family there seems to be an age correlation as regards the onset of the disease.

Chapter III

1. That it should be possible to demonstrate lymphocytosis in relatives of patients with lymphogenous leukemia is shown to be a fallacy. All the reported observations are inconclusive and at most show, now and then, a relative lymphocytosis.

2. The reports in the literature, of coexistence of leukemia and pernicious anemia in the same patient and the same family make it probable that there exists a relation between the two diseases. That this is the case is shown by the fact that the incidence of pernicious leukemia is significantly higher among the relatives of patients with leukemia than among the relatives of the control probands. The author thinks that the relation is due to a common hereditary disposition.

3 A heterologous disposition to various diseases of the blood-forming organs can not be demonstrated. Blood diseases were found to the same extent in the patient material as in the control material, or perhaps it may have been a question of cases that can have been either leukemia or pernicious anemia.

Chapter IV

The literature on the occurrence of Graves' disease, myxedema and diabetes mellitus in patients with leukemia or their relatives is reviewed In the author's material none of these diseases seems with certainty to have a higher incidence than normal, either in the leukemia patients themselves or among their relatives

Chapter V

1 The literature on occurrence of cancer and leukemia in the same patient is reviewed and the uncontrovertible cases of coexistence of the two diseases tabulated in schematic form. Considering that chronic lymphogenous leukemia is more frequent and its age of onset on the average 10 years later than that of chronic myelogenous leukemia, the tendency to oc-

currence concomitantly with cancer seems to be the same for the two types. The frequency of this concomitance seems to be too great to be merely incidental. It is doubtful of skin cancer is particularly frequent in patients with leukemia. The age of onset of the leukemia when associated with cancer does not appear to be earlier than the usual.

2. Among the 4041 relatives of the 209 leukemia patients there were 319 cases of cancer, among the 3641 relatives of the 200 control probands only 218. The higher incidence in the patient material was demonstrable in all the categories of relatives, and likewise there were in the patient material a greater number of families in which the cancer taint was pronounced, than in the control material It is shown that there among the relatives of the leukemia patients was a significantly excessive incidence of cancer as a whole, due to high incidence of all forms of the disease.

The meaning of the term. cancer risk is briefly discussed, and it is shown that the risk of the relatives of patients with leukemia getting cancer is independent of the type of leukemia with which the latter are affected The cancer risk for each category of relatives is calculated and the values found to be between 23 and 48 per cent, with an average of 31 per cent. The figures are minima and rather uncertain, but preassuming that cancer is a disease entity genetically they nevertheless seem rather to point to dominant inheritance of a gene common for all the different forms of cancer.

3. The development of leukemia seems to depend on various conditions, among others on a non-specific hereditary predisposition to cancer, which is believed to be present in at least 20 per cent of the population in general, and partly on one or several genes, the activity of which plays a rôle for the localisation of the cancer to the leukon As leukemia seems to constitute an entity genetically, it is believed that changes in the circumstances of the individual, taken in the widest sense, are determining for the type of the disease which develops. That

external factors play a rôle for the development of the leukemia is evident from the varying times of life at which the disease manifests itself.

While the probability of the occurrence of several cases of leukemia in the same family is rather slight, the risk of near relatives of a patient with leukemia getting cancer is as high as up to 50 per cent. The recognition of this fact may be of importance for the early diagnosis of cancer.

DANISH SUMMARY

Indledning

Afhandlingens Motivering og Maal.

Kapitel I

1. Man anvender den statistisk genealogiske Maade, afgrænser Materialets Omfang med Hensyn til Slægtsstørrelsen og Arten af de i Slægten eftersøgte Sygdomme.

2. De opgivne Cancerdiagnoser kontrolleres i størst muligt Omfang og verificeres for de 427 Personer med en Sikkerhed paa 92 %, *medens man hos 687 Personer, som var opgivet* til ikke at lide af Cancer, kun finder Cancer hos 4

3. Leukæmiens Afgrænsning og Undergrupper omtales Af 310 Leukæmikere lykkes det om Slægten til 209 at faa tilstrækkeligt omfattende Oplysninger Man viser, at disse 209 Probander med Hensyn til Incidens af forskellige Leukæmiformer, Kønsproportion og Aldersfordeling er repræsentative for Sygdommen Leukæmi.

Vanskelighederne ved at opnaa et brugbart Kontrolmateriale omtales Kontrollen omfatter 200 raske Personers Slægtninge. Der vises at være god Overensstemmelse mellem Aldersfordelingen af 4041 Slægtninge i Patientmaterialet og 3641 Slægtninge i Kontrolmaterialet

Kapitel II

1. De i Litteraturen tilgængelige Meddelelser om familiært optrædende Leukæmi gennemgaas kritisk, hvorefter der resterer 26 utvivlsomme Iagttagelser af mindst 2 Leukæmikere i samme Slægt. Disse Iagttagelser gør det sandsynligt, at arvelige Faktorer kan være af ætiologisk Betydning for Leukæmi, men noget overbevisende herom foreligger ikke.

2 Ved Undersøgelse af Slægten til 209 Leukæmikere bestemmes Leukæmiens familiære Incidens til mindst 8,1 %

Flere Leukæmiformer kan forekomme i samme Slægt. Man viser, at den relative Hyppighed af forskellige Leukæmiformer er ens for de familiært optrædende Tilfælde og for Leukæmi i Almindelighed; da man yderligere ikke kan paavise, at der i den enkelte Slægt fortrinsvis forekommer een og samme Leukæmitype, menes Leukæmi i arvebiologisk Betydning at være en Enhed.

For Leukæmiens Vedkommende er der Tale om kromosomal Arv. Leukæmi som saadan arves ikke; man mener, det drejer sig om en arvelig Disposition hertil. Simpel Dominans og Recessivitet kan udelukkes Der er Mulighed for svigtende Dominans eller Polymeri.

Kønsbegrænsning kan udelukkes. Kønsbundethed kan ikke paavises

Man viser, at familiære Tilfælde af kronisk lymfogen Leukæmi manifesterer sig tidligere end sædvanligt for denne Leukæmiform Noget tilsvarende synes trods manglende statistisk Sikkerhed at være Tilfældet for saavel kronisk myelogen Leukæmi som akut Leukæmi. Leukæmi hos Søskende viser sig oftest i nogenlunde samme Alder, ogsaa mellem fjernere beslægtede Leukæmikere synes der at bestaa en Alderskorrelation

Kapitel III

1 Man viser, at Paastanden om, at der blandt Slægtninge til Patienter med lymfogen Leukæmi kan paavises Lymfocy-

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kombinerede Tilfælde ses ikke at optræde tidligere, end Leukæmi sædvanligvis gør det.

2. Blandt 4041 Slægtninge til 209 Leukæmikere findes 319 Cancertilfælde, men blandt 3641 Slægtninge til 200 raske Probander findes kun 218 Cancertilfælde. Cancerovervægten i Patientmaterialet er paaviselig for hver Slægtningegruppe, ligesom der findes flere svært cancerbelastede Slægter i Patientmaterialet end i Kontrolmaterialet. Man viser, at der blandt Leukæmikeres Slægtninge er en signifikant forhøjet Incidens af Totalcancer, beroende paa en høj Incidens af samtlige Cancerformer

Sygdomsrisikobegrebet omtales kort, hvorefter man viser, at Cancerrisikoen for Leukæmikernes Slægtninge er uafhængig af Leukæmiens Art. Cancerrisikoen beregnes for hver Slægtningegruppe. Værdierne ligger mellem 23 % og 48 % og er gennemsnitlig 31 % Tallene er Minimumstal og er behæftede med en betydelig Usikkerhed, men under Forudsætning af, at Cancer udgør en genetisk Enhed, tyder Risikotallene dog nærmest paa dominant Arvegang af et alment Cancergen

3 Udviklingen af Leukæmi synes afhængig af flere Forhold, blandt andet af et uspecifikt Arveanlæg til Cancer, som man mener findes hos mindst 20 % af Befolkningen, dels af eet eller flere Gener af Betydning for Cancerens Lokalisation til Leukon en Da Leukæmi i arvemæssig Henseende synes at udgøre en Enhed, menes Ændringer i Individets Kaar taget i videste Betydning at være ansvarlig for, at snart een, snart en anden Leukæmiform indtræder. Ydre Faktorers Betydning for Leukæmiens Udvikling fremgaar af Leukæmiens varierende Manifestationstidspunkt

Medens der er ret ringe Sandsynlighed for Forekomst af flere Leukæmitilfælde i samme Slægt, naar Cancerrisikoen for en Leukæmikers nærmere Slægtninge helt op mod 50 %. Erkendelse af dette Forhold kan være af Betydning for den tidlige Cancerdiagnose

tose, ikke holder Stik. Alle refererede Undersøgelser er utilstrækkelige og viser højst nu og da en relativ Lymfocytose.

2. Litteratur om Leukæmi og pernicios Anæmi i samme Slægt og hos samme Individ taler for, at der bestaar en Korrelation mellem de to Sygdomme. At dette virkelig er Tilfældet vises derved, at Incidensen af pernicios Anæmi er signifikant større blandt Leukæmikernes Slægtninge end i Kontrolmaterialet. Korrelationen mellem Leukæmi og pernicios Anæmi menes at bero paa et fælles Arveanlæg.

3. Tilstedeværelsen af en heterolog Disposition til forskellige Blodsygdomme kan ikke paavises. I Patientmaterialet findes Blodsygdomme i samme Omfang som i Kontrolmaterialet, eller det drejer sig om Tilfælde, som kan have været enten Leukæmi eller pernicios Anæmi.

Kapitel IV

Litteraturen om Forekomst af morbus Basedowii, Myxoedem og Diabetes mellitus hos Leukæmikere eller deres Slægtninge gennemgaas. Paa eget Materiale ses nævnte Sygdomme ikke med Sikkerhed, hverken hos Leukæmikerne selv eller disses Slægtninge, at forekomme hyppigere end normalt.

Kapitel V

1. Litteratur om Leukæmi og Cancer hos samme Patient gennemgaas. Litteraturens utvivlsomme Iagttagelser af dette Sygdomssammentræf opstilles skematisk. Naar man betænker, at kronisk lymfogen Leukæmi er hyppigere og desuden optræder gennemsnitlig 10 Aar senere end kronisk myelogen Leukæmi, synes de to Leukæmiformer at vise samme Tilbøjelighed til hos samme Individ at kombineres med Cancer. Hyppigheden af Leukæmi og Cancer hos samme Individ menes at overskride tilfældig Sygdomscoincidens. Det er et Spørgsmaal, om Leukæmikere paafaldende ofte faar Hudcancer. De med Cancer

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BIBLIOGRAPHY

(The abbreviations here employed are those adopted by A World List of Scientific Periodicals. Oxford University Press)

1 Ardashnikov, S. N.: Genetics of leukemia in man J Hyg. Camb. 37·286,1937 35, 39, 47, 65, 67, 73

2. Arnsperger, L: Endemisches Auftreten von myeloider Leukämie. München. med Wschr. 52·9,1905. 32, 65

3 Babes: Neoplastische Leukamie Zbl. allg Path path Anat 13·695, 1902. 9

4 Barrenscheen, H K · Zur Frage der akuten Leukämie Wien klin. Wschr. 25:293,1912. 32

5. Bartels, E D. Heredity in Graves' Disease Kbhvn: Munksgaard 1941. Disp Pp 384 p. 78, 137. 11, 79, 80

6 Bauer, J.: Constitution and Disease Lond Heinemann, 1942 p. 177 102

7 Bennet, J H. Case of hypertrophy of the spleen and liver, in which death took place from suppuration of the blood Edinburgh Med. & Surg J 64:314,1845 31

8 Bethell, F H Leukemia: The relative Incidence of Its Various Forms, and Their Response to Radiation Therapy Ann Intern Med *18·757,1943* 54, 89

9 Bethell, F H, C C Sturgis, R W Rundles & M C Meyers Blood A Review of the Recent Literature Arch Intern. Med 77 80, 1946. 69

10 *Bichel, J · Acute leukemia and "achrestic" anemia in a brother and sister Acta med scand 104 578,1940* 42

11. — Lymphatic leukosis influenced by carcinoma of the stomach. Folia haemat. 64 91,1940 86

12. Bie, V: *To Tilfælde af Leukæmi i samme Husstand Ugeskr Læg 72* 1607,1910 37

13 Biermer: Ein Fall von Leukämie *Arch f* path Anat u *Phys 20* 552, 1861. 31, 32

14. *Boggian, B. Quoted by Cotti 27* 35

15 Brandenberg, F: Über familiares Auftreten der chronischen Leukämie Fortschr Med *27*, Nr *31*, *1909* Quoted by Petri 106. 32

16 Braun, E: Gehäuftes familiäres Vorkommen von Pseudoleukämie (malignem Lymphom) und von Sarkom bei erblicher Belastung mit Tuberkulose München. med. Wschr 59.1913,1912 92
17. Brückner· Lymphatische Leukämie und Portiocarcinom. Arch Gynäk 157 616,1934 83
18 Brügger: Familiäres Vorkommen von Leukämie. München med. Wschr. 74 683,1927 32
19. Bugher, J. C. The probability of the chance occurrence of multiple malignant neoplasms Am J Cancer 21 809,1934 91, 84
20 Burg, K M.: Ein mit Radiothor behandelter Fall von myeloischer Leukämie mit komplizierendem Magencarzinom Deuts. med Wschr. 1,881,1924. 85
21 Cabot Case 19341. Hemorrhagic Pleural Effusion associated with a Leukemoid Blood Picture, Reported in Am. J Cancer. 21.490, 1934 85
22 Cameron, I. C.· The influence of leukæmia upon pregnancy and labor. Am J med Sci 85.28,1888 32
23 Campbell. Myelogenous Leukæmia. Lancet. Lond. 90.1473,1912. 32
24 Casali Quoted by Petri 106 32
25 Cicovacki, D Über die Familienuntersuchungen bei der Leukämie unter Berücksichtigung konstitutionell-endokriner Faktoren. Wien. klin Wschr 53 623,1940 36, 47, 66
26. Clemmesen, J. Cancer ventriculi i forskellige Lande. Ugeskr. Læg 108 564,1946 88
27 Cotti, D L. La leucemia a forma familiare. Haematologica 23.1104, 1941 36, 43, 73
28 Craigie, D Case of disease of the spleen, in which death took place in consequence of the presence of purulent matter in the blood Edinburgh Med & Surg J 64.400,1845 31
29 Croq fils Quoted by Petri 106. 32
30 Curschmann, H Über familiäre Leukämie Klin Wschr 15.185,1936 35, 47, 79
31 Dahl, S Spontan Hypoglykæmi Et Tilfælde udviklet hos en Diabetespatient med akut myeloid Leukæmi Ugeskr. Læg. 108·1288, 1946. 76
32 Dalsgaard-Nielsen, T· Endemisk Struma i Danmark. Ugeskr. Læg 102. 845,1940 78
33 Dameshek, W., H A. Savitz & B Arbor Chronic lymphatic leukemia in twin brothers aged fifty-six J Amer Med. Ass 92 1348, 1929 33
34 Danmarks Statistik, Statistisk Aarbog, 1942 p 12 13 98
35 Decapite Quoted by Petri 106 32
36 Decastello, A Akute Leukämie und Sepsis Wien Arch inn Med 11 217,1925 41, 92
37. — Beitrag zur Kenntnis der familiären Leukämie Med. Klin 35: 1255,1939 34
38 Denoyer, A. Carcinoma laringeo in leucemica Ann di laring. otol

36 185,1936, reported in Zbl Hals-, Nasen- u. Ohrenhlk. *28*.171, 1937 86

39. Deutsch, V · Die Bedeutung der Konstitution fur die Entstehung der lymphatischen Leukamie. Mschr. Kinderhlk. *51*.280,1932. 65, 66
40. Dustin, P. Coexistence d'une leucémie lymphoide et d un carcinome gastrique Rev. belge sc med *13*.199,1941 83
41. Elman, C & S Marshall: Anemia of pernicious type complicated by diabetes mellitus and terminating in acute myeloid leukæmia. Lancet Lond *231*.1094,1936 76
42. Eichhorst Pykob. ko racm namar Mcpom *102*·6,1885 Quoted by Petri. 106 32
43. Engelbreth-Holm, J · Leukæmi og anden malign svulst hos samme patient Nord med 9.791,1941. 82-91
44. Eppinger· Uber akute myeloischer Leukamie Wien. klin Wschr. *24*: 1655,1911 32
45. Ferrero, A & L Gedda. Sull'associazione clinica dei processi neoplastici e leucemici Cancro *4*·76,1933 Reported in Amer J. Cancer *21*:248,1934 86
46. Fisher, R A Statistical Methods for Research Workers London Oliver & Boyd 9th ed 1944 p 85-99
47. Fisher, R A & F Yates. Statistical tables for biological, agricultural and medical research Lond Oliver & Boyd 1938 p 27.
48. Forkner, C E Leukemia and allied disorders New York· Macmillan Co 1938, p 95 17, 76
49. Fuhs, H. Multizentrische Basalzellenepitheliome bei lymphatischer Leukamie Derm Wschr *85* 1533,1927 83
50. Gertler Lymphatische Leukamie bei gleichzeitigen Haut-Carcinomen Zbl Haut u Geschlkr *68* 271,1942 83
51. Goldstein, H I Acromegaly with leucemia and acromegaly of the larynx Med J & Record *134* 395,432,1931 77
52. Gottlebe, P. Ueber familiares Vorkommen von Leukamie Munchen med Wschr *85* 140,1938 40, 66
53. Gram, H. C & R Nielsen Leukæmiens Forekomst i Danmark Ugeskr Læg *94* 437,1932 53
54. Greene, J L Acute leukæmia during pregnancy N Y Med J *47*: 144,1888 32
55. Gansslen, M Erbpathologie des Blutes und der blutbildenden Organe Bauer, Fischer, Lenz (editt) Hdb d Erbbiol d Mensch IV/1 5te Aufl Berlin 1940 p 468 36, 38
56. Haden, F H The Leukemias Cleveland and Clin Quart *11* 55,1944. Quoted by Bethell et al 54
57. Hald, A Statistiske Metoder (in the press) 94
58. Halșe Quoted by Gansslen 73
59. Hanzel, F.: Zur Diagnose der akuten lymphoiden Leukamie im Rachen Wien klin Wschr *21* 594,1908 32, 79
60. Hart, J F L, J R Lisa & P A Riedel Diabetes mellitus complicated with lymphatic leukemia Report of a case with autopsy J Amer Med Ass *113* 1222,1939 76

61 Heim Myeloische Leukämie und Uteruskarzinom Zbl Gynäk 57,1840, 1933 85

62 Hering, E M Ein Beitrag zur chronischen Leukämie unter besonderer Berücksichtigung der Erblichkeit und des Auftretens im höheren Lebensalter Lpz. 1935 Pp 51 Inaug Diss 34

63 Hirschfeld, H. Leukämie und verwandte Zustände in Schittenhelm, A · Hdb d. Krankheiten d Blutes u d blutbild Org Bd I Berlin Springer 1925 p 431 32

64 — Blutkrankheiten und Konstitution in Klemperer· Neue deutsche Klinik 13 523,1935 73

65 Hofmeier, K. Die Bedeutung der Erbanlagen für die Kinderheilkunde Beiheite zum Arch Kinderhlk 14 153,1938 36

66 Hoffmann, W J · Quoted by Schreiner, B F & W. H. Wehr. 123 86

67 Hogreffe, G Familial occurrence of leukemia Acta path et microbiol scandinav. 22 89,1945 45, 49, 92

68 Hornbaker, J. H · Chronic Leukemia in Three Sisters J Amer Med Ass 203 332,1942 44

69 Hotz, A Zur Differentialdiagnose Agranulozytose-Leukämie Z. Kinderhlk 62 529,1941 83

70 Hultkrantz, J V. & Dahlberg· Die Verbreitung eines monohybriden Erbmerkmals in einer Population und in der Verwandtschaft von Merkmalsträgern Arch Rass- u Ges Biol 19 129,1927 101

71 Jacques Quoted by Hering 62 35

72 Jacobsen, O Heredity in Breast Cancer Kbhvn · Nyt Nordisk, Lond. Lewis & Co 1946 Pp 306 10, 11, 92, 98, 102

73 Jelke, H Akute lymphatische Leukämie bei eineiigige Zwillingen Acta prædiat 27,87,1940 42

74 Jewett, C S. Notes on Leukemia with Report of Three Cases Philadelphia Med J 7 816,1901 32

75 Joslin, E P The Treatment of Diabetes Mellitus 5th ed Lond: Kimpton 1935 p 408 76

76 Kast, H-W Leukämoide Reaktionen bei malignen Tumoren Deuts Arch klin Med 188 173,1942 83

77 Kellet Quoted by Schulten, H 128 49

78 Kemp, T Polymerism in morbid inheritance Hereditas 29 76,1943 53

79 Kirshbaum, M J & F. S Preuss Leukemia A clinical and pathologic study of one hundred and twenty-three fatal cases in a series of 14400 necropsies Arch Intern Med 71 777,1943 54, 77, 86, 87

80 Koehler, G D Atypische myeloische Leukämien (Erythrämische Reaktion) Klin Wschr 7 1186,1928 34, 67

81 Korteweg, R Over myeloide leukaemie bij zuilingen Ned Tijdschr Geneesk 63 638,1919 34

82 Kraupse Quoted by Gänsslen 55 36

83 Kreibig W Über multiple Geschwulstbildung im Darmtrakt Deuts Z. Chir 219 334,1929 84

84 Lannois, M & C Regaud Coëxistence de la leucocythémie vraie et d'un cancer épithélial Arch med exp 7 254,1895 83

18*

85. Laub, R.: Ueber familiäres Auftreten der Leukämie. Schweiz med. Wschr. 69·71,1939. 40
86 Leube, W von: Rapid verlaufende schwere Anämie mit gleichzeitiger leukämischer Veränderung des Blutbildes. Berl. klin Wschr. 37: 851,1900. 68
87. Levi, J. E. & H. T. Friedman: Insulin resistence in a case of diabetes mellitus and chronic lymphatic leukemia New England J Med 225.975,1941. 76
88 Lossen, J.: Zum familiären Auftreten der myeloischen Leukämie Med. Welt. 16:467,1942 44
89. Maack, W Familiäre Leukämie und wiederholtes Auftreten von Diabetes, Morbus Basedow in Leukämikerfamilien Greifswald: Adler 1940 Pp 21. Inaug Diss 36, 42, 79, 92
90. Maciotta, G.. *Contributo clinico, etiopathogenetico, et anatomopathologico allo studio delle leucemie acute nei bambini* Zbl. ges. Kinderhlk 22·429,1929 34
91 Mannaberg· Quoted by Petri 106 32
92 Marischler, J.: Ein Fall von lymphatischer Leukämie und einem Grawitz'schen Tumor der rechten Niere Wien. klin Wschr 9·986, 1896 83
93 McGavran, C W Three Cases of Leukemia in one Family Amer J. med. Sci 164 545,1922 37
94 Meikle, R W Two Varieties of Leukemia in one Family. Brit. Med J 99(II) 468,1944 44
95 Miller, F R & D. L Turner The Leukemias Med Clin North. America 28 1376,1944 9
96. Minot, G R & R. Isaacs: Quoted by Forkner 48 89
97 Moeschlin, S & K Rohr· Klinische und morphologische Gesichtspunkte zur Auffassung des Myelose als Neoplasma Ergebn inn Med. Kinderhlk 57·723,1939 45, 86, 87
98 Mohr, W Lymphatische Leukämie und Erblichkeit Deuts med Wschr 64 704,1938 36, 66
99. Morawitz, P: Erblichkeit und Konstitution bei Leukämien München med Wschr 80·1201,1933 38
100 Morrison, M, F Feldman & A A Samwick· Carcinoma and leukemia *Report of two cases with combined lesion Review of literature* Ann Intern Med 20 75,1944 83, 85
101. Naegeli, O: Leukaemia Ergebn ges Med 1 1,1920 78
102 — Blutkrankheiten und Blutdiagnostik 5 Aufl Berlin Springer 1931 p 447 34
103 Ortner, N Beitrag zur Leukämie im Kindesalter Jahrb Kinderhlk 32:252,1891 32
104. Ovnbol, A & K Terkildsen Et tilfælde af sarcom, *carcinom* og leukose hos samme patient Nord Med 20 1662,1943 83
105 Penzold, H· Leukämie und Carcinom Deuts Arch. klin Med 180 430, 1937 83
106 Petri, S.: Über familiäres Auftreten der Leukämie Acta path. et microbiol scandinav 10·330,1933 32, 37, 38, 47, 52, 73

107. Postel, Z.· Leukämie und Vererbung Ein Bericht über aleucämische Myelose bei zwei Schwestern. Z. menschl. Vererb. u Konstitutionslehre *25* 518,1942 36
108 Presnyakov. Quoted by Ardashnikov 1 67, 68
109 Pulvertaft, R. J. V: Multiple primary epithelioma in lymphatic leukemia Brit. J. Surg *24* 50,1936 Reported in Index analyt. cancerl *11* 292,1937 83
110 Reich, C.. A case of adenocarcinoma of the sigmoid with lymphatic leukemic blood picture Amer J. Cancer *26* 781,1936 83
111 Ribbert, M W H: Geschwulstlehre für Aerzte und Studierende Bonn· Cohen 1904 9
112 Riccitelli, L. & E Ragnotti· Sulla leucemia familiare. Ann. Fac. Med Perugia *30* 25,1927. 37
113 Rich, M L. & L. Schiff. A case of pernicious anemia and chronic lymphatic leukemia. Ann Intern. Med *10* 252,1936/37 68
114 Richards, C · Two cases of lymphatic disease in the same family, with Roentgen findings Amer J. Roentgenol. *8* 514,1921. 92
115 Rohr, K.· Ueber den Beginn und die Vererbung der chronischen myeloischen Leukämie Schweiz. med Wschr *75* 1042,1945 37, 45, 92
116 Rosenhaupt, H.. Kasuistischer Beitrag zur Vererbungsfrage bei der akuten Leukämie Zbl Kinderhlk *20* 208,1915 34
117 Rosenow, G · Blutkrankheiten. Berlin. Springer 1925 p 124 37, 47
118 Rosenquist, K . Endemisk Struma i Danmark Ugeskr Læg *102* 906, 1940 78
119 Saar v · Quoted by Kreibig 83 86
120 Schemm, F R A pernicious family Five authenticated cases in the same generation. Amer J Med Sci *199* 167,1940 48
121 Schereschewsky, E Über einen Fall von Geschwisterleukämie Zbl inn Med *47* 643,1926 37, 79
122 Scheuffler, A: Carcinombildung auf einen Leukämid Arch Derm. Syph Wien *168* 586,1933 83, 88
123 Schreiner, B F & Wehr Lymphatic leukemia associated with cancer; 4 cases Amer. J Cancer. *21* 368,1934 83, 86, 87
124 Schinz, H & F. Buschke. Krebs und Vererbung Thieme Lpz 1935 Pp 280 102
125 Schmorl Über akute myeloischer Leukämie Zbl allg path Anat 22· 906,1911. 32
126 Schnyder· Ueber einen Fall von akuter aleukämischer Myeloblastenleukämie Schweiz med Wschr. *18* 316,1937 39
127 Schuback, A Ein Kollisionstumor des Magens Z. Krebsforsch 33·126, 1931 84
128 Schulten, H Lehrbuch der klinischen Hämatologie Zweite Aufl Lpz: Thieme 1943 Pp 479, p 160, 328 72
129 Schulz, F Perniziöse Anämie mit Ausgang in Mikromyelobelastenleukämie Klin Wschr. 20 264,1941. 68
130 Schumann, C Pernicious anemia with diabetes, leukemia in a daughter J Amer med Ass 85 677,1925 67, 79

131 Seiler, J: Zur Frage der reaktiven Blutkrankheiten Deuts. Arch klin Med. 177.170,1935 35, 73
132 Senator· Zur Kenntnis der Leukamie und Pseudoleukämie im Kindesalter Berl klin. Wschr. 35.533,1882. 32
133. Shal, G. F.. Two cases of lymphatic leukemia associated with malignant tumors Klin med 11 1149,1933 86
134 Sheldon, J. H: Diabetes insipidus occurring in case of lymphatic leukemia of aleukaemic type Lancet, Lond 1 489,1927. 76
135 Shipton, E A Familial Leukosis, Med J. Australia 25·116,1938 35, 40
136. Siegel, A E Lymphocytic Leukemia occurring in Twins, Atlantic Med J 31 748,1928 34
137 Stamos, H F· Heredity in pernicious Anemia Amer J med Sci 200. 586,1940 48, 67
138 Steiner, F Familiare Leukamie Munchen med Wschr 80:1822, 1933. 38, 47
139 Sterne, E H, H Schiro & W Molle Pernicious anemia complicated by myelogenous leukemia Amer J med Sci 202 167,1941 68
140 Strandell, B Akute Mikropromyelozyten-leukamie und perniziose Anamie in derselben Familie Acta med scand 87 557,1935/36 67
141 Strandell, B & R Lemming Pernicious Anemia and Myelocytic Leukemia in Two Brothers Acta med scand 75 21,1931. 67
142 Stromgren, E Zum Ersatz des Weinbergschen "abgekurzten Verfahrens". Z ges Neurol Psychiat 153 784,1938 11, 98
143 Thiele, W Perniziose Anamie und Magencarzinom Klin Wschr 17 1253,1938 72
144 Touw, J F & C A Graafland A case of aleucemic lymphatic leucemia with specific localizations and symptomatic pernicious anemia Acta med scand 102 124,1939 68
145 Turpin, R Coincidences familiales de leucémie aigue et de sleroderrmie Pr med 52 51,1944 37
146 Vercellotti, G Linfoadenosi leucemia famigliare Clin med ital 57 437,1926 37
147 Virchow, R Weisses Blut Froriep's Notizen 33 151,1845 31
148 Vollenweider, P Uber familiares Auftreten von angeborener Leukamie Zurich Thalwil 1914 Pp 32 Inaug Diss 33
149. Waaler, G Om kreft og arvelighet Nord med tidskr 4 761,1932 10, 102
150 Wainwrigth, I M A comparison of conditions associated with breast cancer in Great Britain and America Amer J Cancer 15 2610, 1931 10
151 Ward, G Infective theory of acute leukemia Brit J Child Dis 14 10,1917 89
152. Warwick Multiple primary malignant growth Proc Roy Soc Med 24:206,1931 84
153. Wassink, W F· Cancer et hérédité Genetica 17 103,1935 10
154 Weinberg, W Zur Probandemethode Arch Rassenbiol 23 281,1931 11, 98

155 Weiss, J Ueber die akute myeloische Leukämie. Wien klin Wschr 24 1656,1911 37, 41
156 — Über ...... akuter Leukämie und septischen Infekt. Wien Arch. inn Med 14 303,1927 41
157 Weitz, W.. Die Vererbung innere Krankheiten in Bauer-Fischer-Lenz (editt): Menschliche Erblehre und Rassenhygiene I/2 Fünfte Aufl. Berlin: 1940 p 256 36
158 Werner, W.. Über die Erblichkeit der perniziösen Anämie auf Grund von klinischen Untersuchungen in 57 Sippen Verh deuts Kongr. inn Med 50 303,1938 48, 67, 68
159 Whipham, T· Splenic leukæmia with carcinoma Trans. Path. Soc Lond. 29 313,1878 85
160 Winkler, P: Über familiäre Leukämie Köln· Borowsky 1939 Pp 54 Inaug Diss p 55 39, 65
161 Wolff, E Agranulocytose und Myeloblastenleukämie als Reaktionsformen auf denselben Infekt bei zwei Geschwestern Folia haemat 44 38,1931. 73
162 Woolley, P. B Myelogenous leucæmia complicating pernicious anæmia Lancet, Lond 246 85,1944 68
163 Wright Clifton Med Bull 14 1,1928, quoted by Hart, Lisa, Riedel 60 76
164 Wullenweber, G Über familiäre Leukämie Deuts med Wschr 63 488, 1937 39, 79
165 Yang, C-S Chronic myelogenous leukemia in association with lymphosarcomatosis and transient diabetes insipidus Chinese med J 50 1153,1936 76
166 Zadek, I Radiothorium bei leukämischer Myelose Folia haematol 154 330,1933 85, 86, 87